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archives of Otolaryngology—Head & Neck Surgery

Communicative Disorders **Facial Plastic & Reconstructive Surgery**

4

Antibiotic-Induced Hearing Loss

Cochlear Microcirculation

Prevalence of Tinnitus

Rhabdomyosarcoma in Children

Patterns of Node Metastases

Carotid Body Paragangliomas

Mandibular Tumor Invasion

Snoring Can Be Reduced

Official Publication for
American Academy of Facial Plastic and Reconstructive Surgery,
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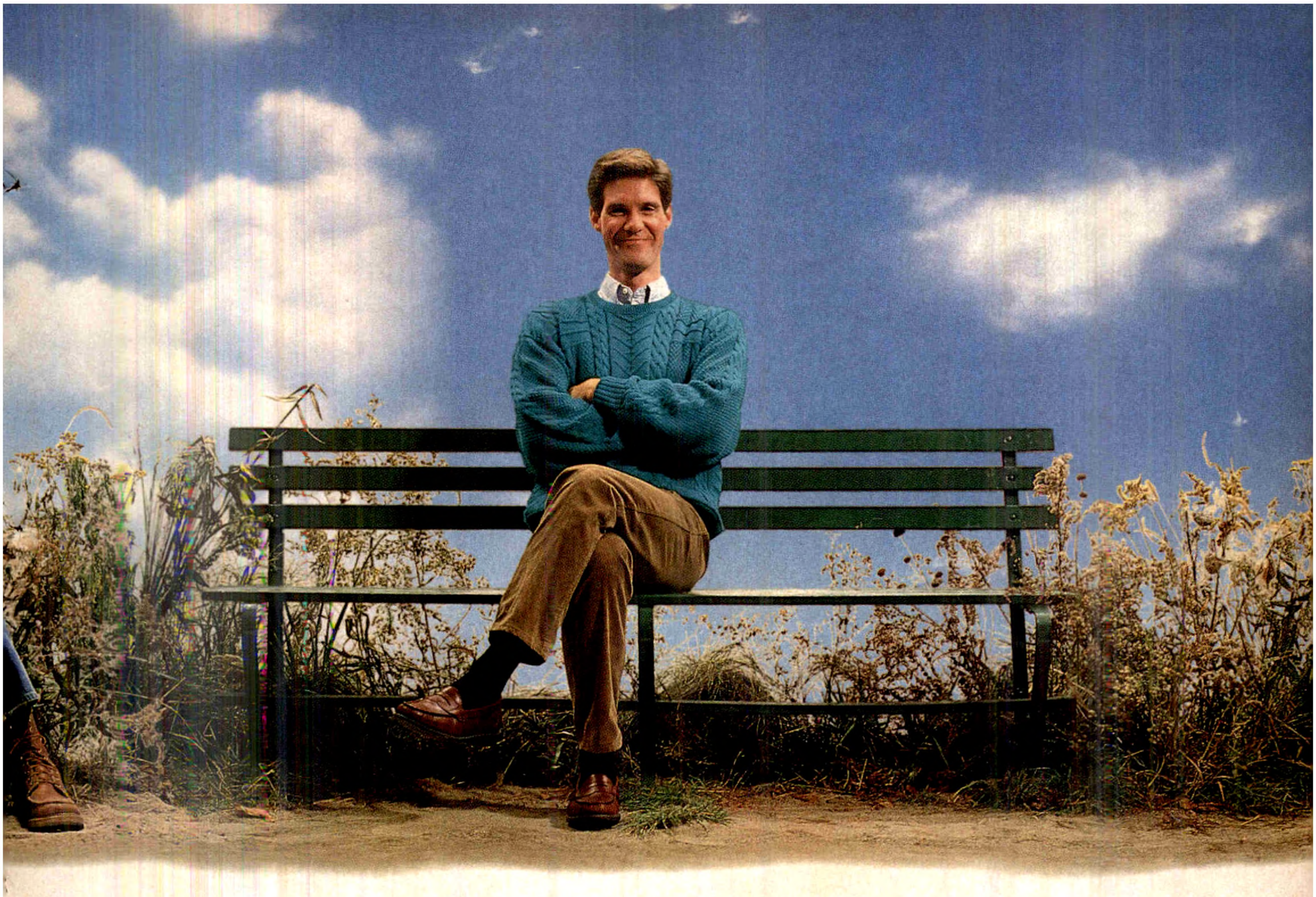

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Beconase AQ® Nasal Spray, 0.042%* **SHAKE WELL BEFORE USE.**
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The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2-1006 March 1989

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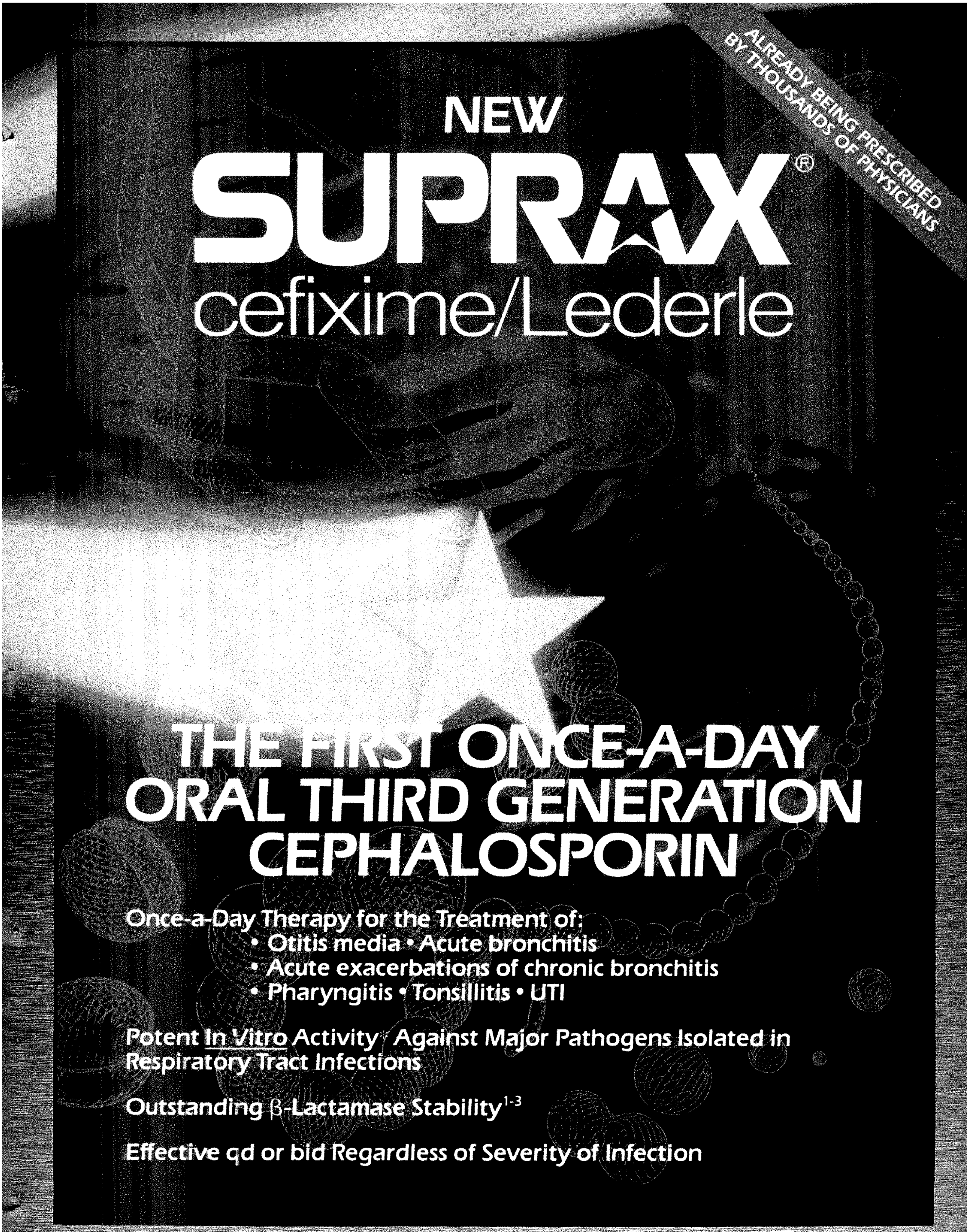

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1. Sanders CC: β-Lactamase stability and in vitro activity of oral cephalosporins against strains possessing well-characterized mechanisms of resistance. *Antimicrob Agents Chemother* 1989;33:1313-1317. **2.** Neu HC: *In vitro* activity of a new broad spectrum, beta-lactamase-stable oral cephalosporin, cefixime. *Pediatr Infect Dis J* 1987;6:958-962. **3.** Neu HC, Chin N-X, Labthavikul P: Comparative *in vitro* activity and β-lactamase stability of FR 17027, a new orally active cephalosporin. *Antimicrob Agents Chemother* 1984; 26:174-180.

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Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *B catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *B catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime[a] 4 mg/kg bid	Cefixime[a] 8 mg/kg qd	Control[a] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[b]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

[a] Number eradicated/number isolated

[b] An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest***, Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix*** or Tes-Tape***).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics, therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (4%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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CHARLES M. STIERNBERG, MD, SECTION EDITOR
University of Texas, Galveston

Pulsed-Dye Laser Treatment for Facial Vascular Lesions

William H. Beeson, MD, Indianapolis, Ind, and W. Russell Ries, MD, Nashville, Tenn, addressed the Southern Section meeting of the American Academy of Facial Plastic and Reconstructive Surgery in White Sulfur Springs, WVa, on January 11, 1990, concerning the use of the tunable pulsed-dye laser for vascular lesions of the skin. They reported that this was a specially developed laser powered by a flash lamp using fiberoptic cables to a handpiece. Ideally, a laser used to treat skin lesions would have properties that would cause damage to the intimal layers of the vessel and yet spare the dermis and epidermis. The selective photothermolysis properties of this laser were developed to be wavelength specific and directed at the oxyhemoglobin target. The wavelength most appropriate was 585 nm, and it appeared that the optimal duration was 300 to 400 milliseconds with a 5-mm-diameter spot size. They reported that this pulsed-dye laser worked best for port-wine stains, hemangiomas, and some telangiectasias. This procedure was felt to be contraindicated in persons with known photosensitivity to this wavelength laser, in persons receiving anticoagulants, and in those individuals with light-induced seizure disorders, and relatively contraindicated in dark-pigmented individuals since the melamin tended to interfere with the absorption of the energy. Patient counseling and photodocumentation was felt to be essential in using this pulsed-dye laser for facial skin lesions. In addition, each patient should have a test spot treatment with the pulse-dye laser prior to full treatment. This test spot is used to determine the outcome with varying lengths of exposure time and spot size.

After 6 weeks, adjustments and treatments can be made based on these test spots. Retreatments can then be performed every 6 to 8 weeks until the lesions are eradicated. The authors felt that it was very important not to overlap the spots. The treatment results were better if the areas were retreated with the smaller spot size in 6 to 8 weeks.—CDR Gregg S. Parker, MC, USN, Portsmouth, Va

Blepharoplasty in the Elderly Patient With Senile Lower Eyelid Changes: Combined Transconjunctival and Lateral Strip Technique

At the Southern Regional Scientific meeting of the American Academy of Facial Plastic and Reconstructive Surgery, Dr Ira D. Papel, Baltimore, Md, White Sulfur Springs, WVa, described several of the most common undesirable appearances of the eyelids after lower blepharoplasty. Scleral show, rounded palpebral fissure, and ectropion in the senile lower eyelid can be minimized by careful preoperative evaluation and selection of one of several procedures designed to tighten or suspend the lower eyelid.

The lower blepharoplasty procedure preferred by the author for the senile lower eyelid is the combined transconjunctival and lateral strip technique. A 1-cm lateral canthotomy is performed, transecting the inferior crus of the lateral canthal tendon. Fat removal is accomplished by incising the conjunctiva and approaching the orbital fat either through the orbital septum or behind the septum. The conjunctiva is then closed with a running 6-0 mild chromic suture in a subconjunctival plane. The lateral tarsal plate is de-epithelialized and suspended in a superior lateral direction with a prolene mattress suture, being careful to overcorrect 2 to 3 mm. Finally, the skin is redraped and the excess is excised.
—LCDR Stephen B. Freeman, MC, USN, Portsmouth, Va

Angioedema From Angiotensin-Converting Enzyme Inhibitors: A Cause of Upper Airway Obstruction

At the recent meeting of the 1990 Southern Section of the Triological Society in White Sulfur Springs, WVa, Thomas L. Eby, MD, in conjunction with Timothy H. Gannon, MD, both of Birmingham, Ala, presented four cases of angiotensin-converting enzyme inhibitor-induced angioedema in which significant upper airway obstruction was involved.

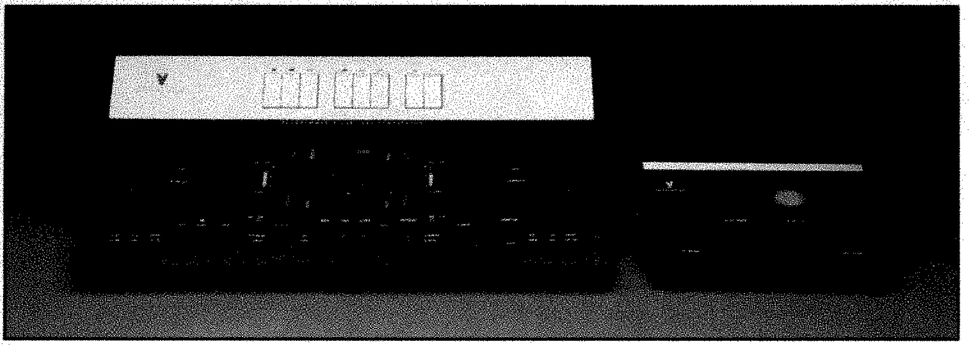
A detailed review of the mechanism of induction of angioedema in these patients was presented. It appears that there is a potentiation of the inflammatory mediator bradykinin that results in vasodilation, increased vascular permeability, and, thus, the angioedema. Since this angioedema can progress to upper airway obstruction, all otolaryngologists should be aware of this association. The authors note that it is important in patients who present with angioedema to question the patient about the use of angiotensin-converting enzyme inhibitor medications.
—LCDR Kevin S. Kennedy, MC, USNR, Portsmouth, Va

Anatomic Nuances of the Ostiomeatal Complex of Importance to the Endoscopic Sinus Surgeon

At the recent meeting of the 1990 Southern Section of the Triological Society in White Sulfur Springs, WVa, Steven

(Continued on p 391.)

THE EQUIPMENT



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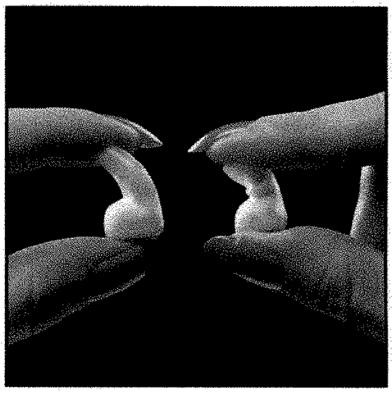

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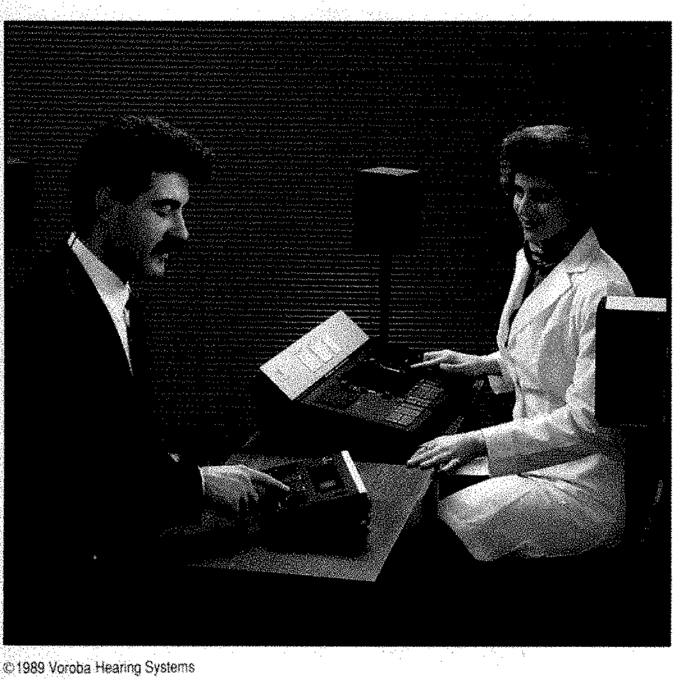

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(Continued from p 389.)

Sobol, MD, presented a paper in conjunction with Mark May, MD, in which they attempted to clarify some of the nuances of the anatomical variations encountered in functional endoscopic sinus surgery. They feel that a detailed awareness of the anatomy involved in these surgical procedures will help to prevent the complications that may be encountered.

They especially feel that a sharpened awareness of the anatomy of the infundibulum and the natural ostium helps to prevent intraorbital inocular complications. In an effort to define the infundibulum and its boundaries and to clarify the location of the natural maxillary ostium, a three-dimensional study was undertaken of 10 parasagittally-sectioned cadavers, as well as an additional 30 subjects who were studied endoscopically. The anatomical relationships were documented and presented to the Southern Section.

Following careful infundibulotomy, the natural ostium is identified early, prior to removal of other structures. The relationship of the natural ostium to the orbit is important to keep in mind. It is located at the junction of the medial antral wall roughly halfway between the distance between the anterior and posterior maxillary sinus walls. Often accessory os are noted posteriorly and inferiorly to this landmark, and these need to be recognized as such. From the intranasal aspect, this os can be found directly posterior to the cut edge of the uncinate process.

It is noted that blind probing superior to this level with a biting forceps will invariably lead to herniation of orbital fat and possible intraorbital bleeding. It is felt that the infundibulum has been poorly defined in the existing literature. The infundibulum is a complicated three-dimensional space that should be thought of as a cavelike recess that communicates with the middle meatus via the hiatus semilunaris, whose anteromedial and anteroinferior boundaries are aspects of the uncinate process, the posterior boundary of which is the bulla ethmoidalis. The lateral boundaries are composed of the orbit and its membranous fontanelles. The infundibulum, of course, serves as a confluence of drainage for maxillary, anterior ethmoid, and frontal sinuses. The authors conclude that detailed anatomic awareness of the relationships of three-dimensional structures surrounding the maxillary sinus natural ostium is of key importance in preventing orbital and ocular complications when performing functional endoscopic sinus surgery.—LCDR KEVIN S. KENNEDY, MC, USNR, Portsmouth, Va

In Other AMA Journals

JAMA

Multivitamin/Folic Acid Supplementation in Early Pregnancy Reduces the Prevalence of Neural Tube Defects
A. Milunsky; H. Hick; S. S. Jick; C. L. Bruell; D. S. MacLaughlin; K. J. Rothman; W. Willett (*JAMA.* 1989;262:2847)

Underreporting of AIDS Cases in South Carolina, 1986 and 1987
G. A. Conway; B. Colley-Niemeyer; C. Pursley; C. Cruz; S. Burt; P. Rion; C. W. Heath, Jr (*JAMA.* 1989;262:2859)

Public Policy and the Supply of Primary Care Physicians
P. G. Barnett; J. E. Midtling (*JAMA.* 1989;262:2864)

A Parting Shot at Tobacco
C. E. Koop (*JAMA.* 1989;262:2894)

Does Silicosis Still Occur?
D. Valiante; K. D. Rosenman (*JAMA.* 1989;262:3003)

Unanticipated Admission to the Hospital Following Ambulatory Surgery
B. S. Gold; D. S. Kitz; J. H. Lecky; J. M. Neuhaus (*JAMA.* 1989;262:3008)

Randomized, Controlled Trial of Clonidine for Smoking Cessation in a Primary Care Setting
P. Franks; J. Harp; B. Bell (*JAMA.* 1989;262:3011)

Fifty Hours for the Poor
G. D. Lundberg; L. Bodine (*JAMA.* 1989;262:3045)

Hooked on Hormones?
E. B. Kashkin; H. D. Kleber (*JAMA.* 1989;262:3166)

12
11
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8
6

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(terfenadine) 60 mg tablets BID
for seasonal allergic rhinitis

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Before prescribing Seldane, please see Brief Summary of Prescribing Information, which appears on the reverse side.

Seldane®

(terfenadine) 60 mg Tablets

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients: Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility: Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C: There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use: Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General: Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia, torsade de pointes and ventricular fibrillation), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of January, 1990 Y460D
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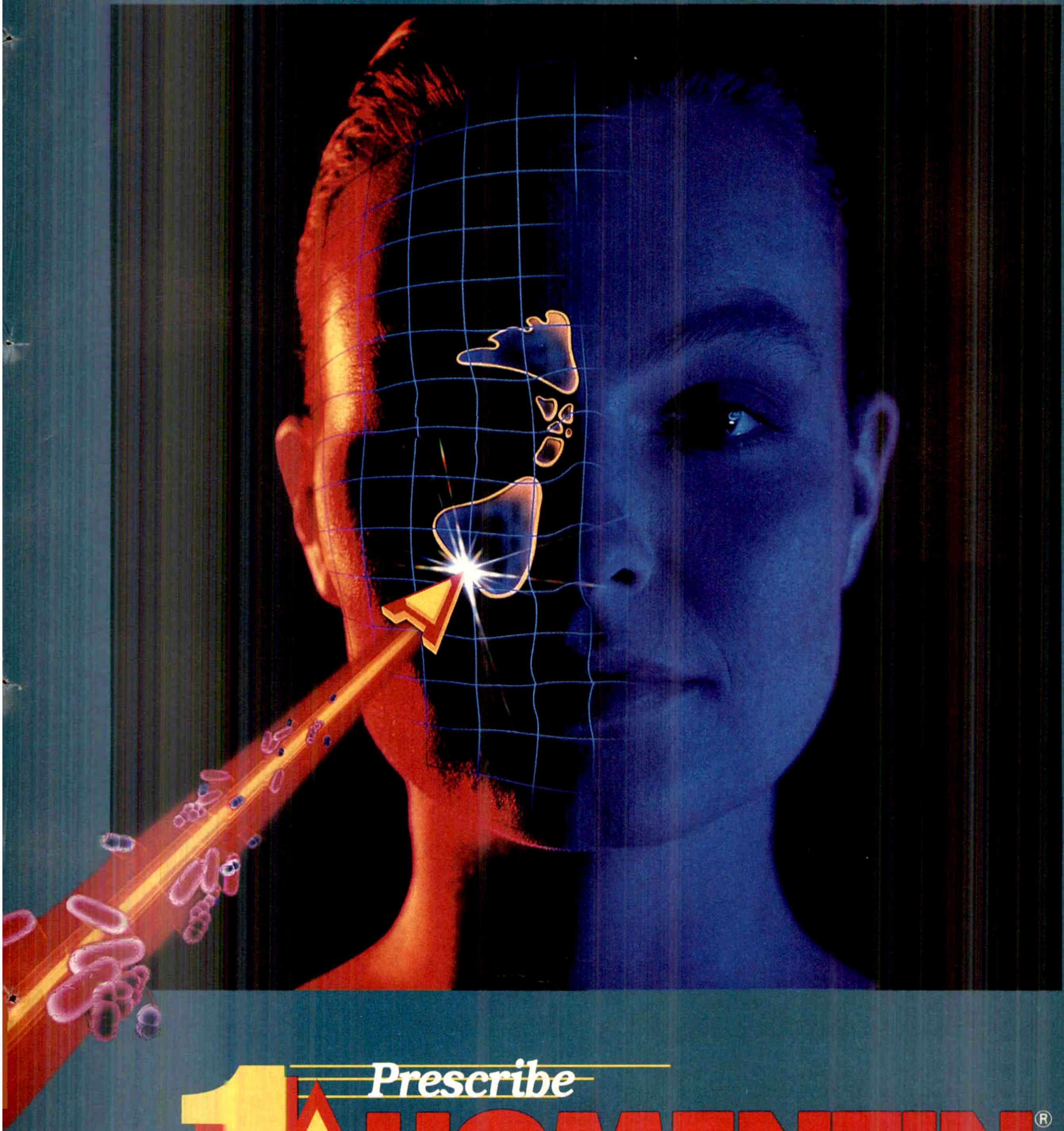

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amoxicillin/clavulanate potassium

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Please see brief summary of prescribing information on adjacent page.

Brief Summary of Prescribing Information

AUGMENTIN® amoxicillin/clavulanate potassium

Indications and Usage: AUGMENTIN* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to AUGMENTIN treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to AUGMENTIN, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to AUGMENTIN when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While AUGMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN and allopurinol administered concurrently.

AUGMENTIN should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to AUGMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of AUGMENTIN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when AUGMENTIN is administered to a nursing woman.

Adverse Reactions: AUGMENTIN is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%), and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT and/or SGPT has been noted in patients treated with ampicillin class antibiotics as well as with AUGMENTIN, but the significance of these findings is unknown. As with some other penicillins, and some cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with AUGMENTIN.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one AUGMENTIN '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one AUGMENTIN '500' tablet every eight hours.

Since both the AUGMENTIN '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two AUGMENTIN '250' tablets are not equivalent to one AUGMENTIN '500' tablet. Therefore, two AUGMENTIN '250' tablets should not be substituted for one AUGMENTIN '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as AUGMENTIN '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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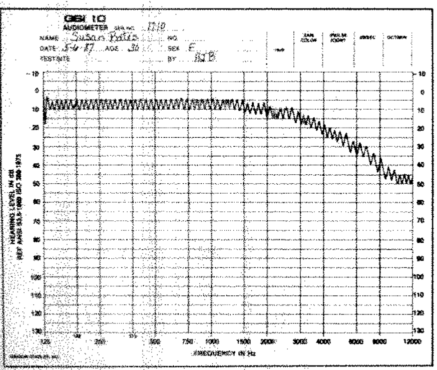

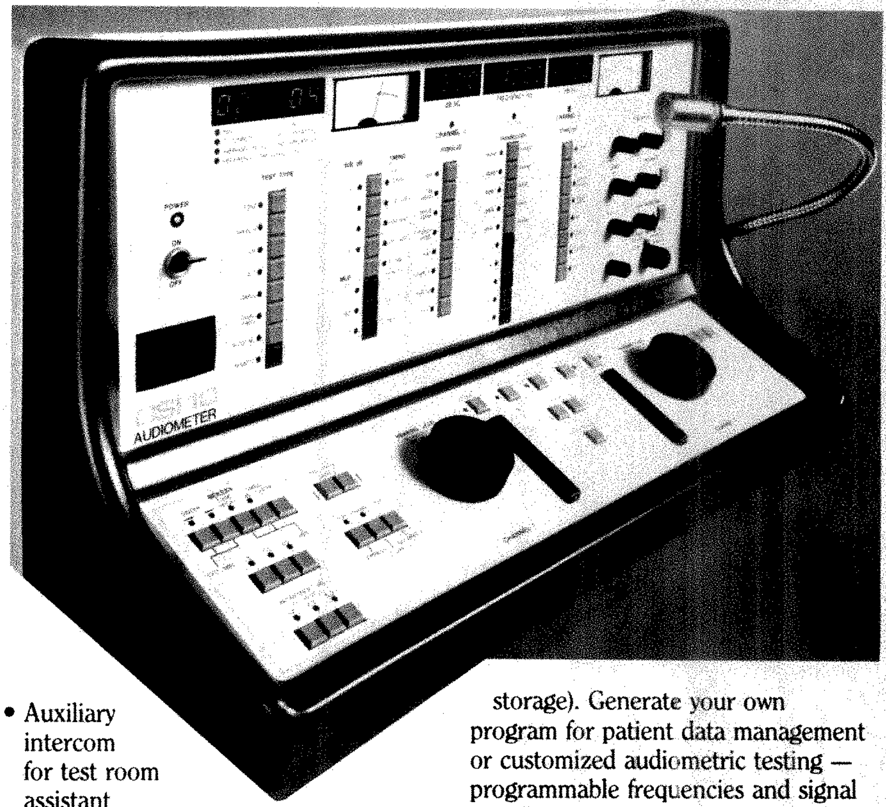

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Facial Plastic News

WAYNE F. LARRABEE, MD, SECTION EDITOR
Virginia Mason Clinic, Seattle, Wash

Oculoplastic Surgery

Among the many excellent presentations at the recent International Symposium in Toronto, Canada, were several from the American Society of Ophthalmic Plastic and Reconstructive Surgeons. These included a discussion of lower eyelid stability and lower eyelid malposition by John W. Shore, MD, Boston, Mass, and correction of lower eyelid position by Arthur J. Shaefer, MD, Buffalo, NY.

In his presentation, "The Importance of Lower Eyelid Stability in the Prevention and Correction of Lower Eyelid Malposition," Dr Shore discussed the forces acting on the position of the lower eyelid in a superior, horizontal, inferior, or posterior direction.

The levator muscle and the preseptal and pretarsal orbicularis oculi muscle pull the lower eyelid in a superior direction. Due to its long elastic tendon, the levator muscle can transfer force through the lateral canthal tendon and raise the lower eyelid. Tightening of the preseptal and pretarsal orbicularis oculi muscle exerts force on the lid in several directions. With contraction, as in normal blinking, the lower eyelid is pulled superiorly with the eyelid margin tightened in a horizontal direction and pulled posteriorly against the globe.

There are several forces that act on the eyelid in an inferior direction. Gravity is the first major force that is constantly acting to pull the eyelid downward. Along with increasing laxity of the supporting tissues with age, gravity has the potential to produce such malformations as lower eyelid ectropion. The lower eyelid retractors, including the capsulopalpebral fascia and the inferior tarsal muscle, provide the second major inferior force on the lid. The capsulopalpebral fascia is found beneath the orbital fat of the lower eyelid and is equivalent to the levator aponeurosis of the upper eyelid. It extends from the inferior border of the tarsus to the suspensory ligament of Lockwood and is the principal lower eyelid retractor. The inferior tarsal muscle is a nonstriated muscle somewhat similar to Müller's muscle in the upper eyelid. It originates from the inferior rectus muscle and extends forward to insert on the inferior border of the lower tarsus. A third force contributing to inferior pull on the eyelid includes the muscles of facial expression that extend from the lower face to the orbicularis oculi muscles. The last factor that can produce a downward force on the lower eyelid is a pronounced proptosis. With enough protrusion, the orbit can mechanically force the eyelid downward. Alone or in combination, all of these factors may produce a major eyelid instability producing such deformities as lower eyelid ectropion or entropion.

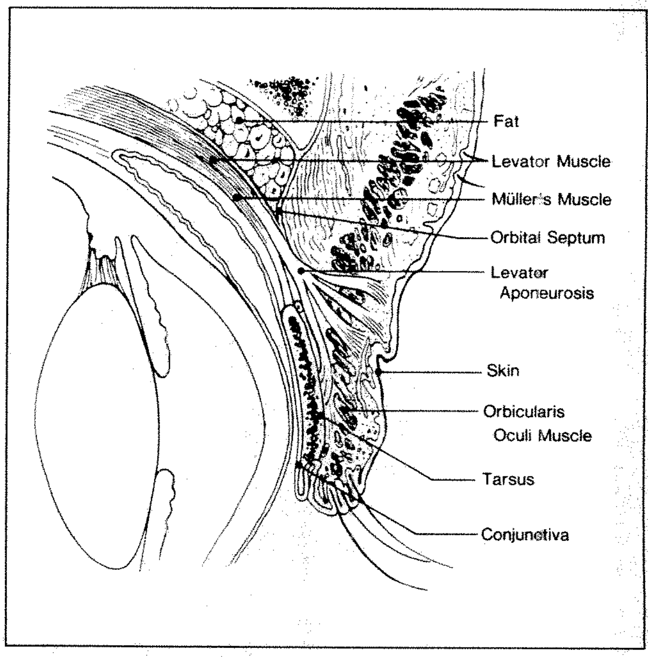
Last, several factors may act to pull the eyelid in a posterior direction. The tarsoligamentous sling acts in a posterior direction by pulling the eyelid back against the globe. The lower eyelid retractors also exert some posterior pull on the eyelid in addition to their strong inferior pull. The orbicularis oculi muscle, as previously noted, also exerts a posterior pull on the eyelid with blinking.

The sum of all these forces should produce a stable eyelid with good tone, good position, and normal apposition of the eyelid to the globe. Eyelid laxity, scarring, proptosis, and lower eyelid retractor dehiscence can produce an unstable eyelid with various degrees of ectropion or entropion. The goal of surgery is to correctly analyze the etiology of an unstable eyelid and then take measures to correct it.

Dr Shaefer then followed with his presentation, "Correction of Lower Eyelid Malposition: Entropion, Ectropion, and Lower Eyelid Retraction." He emphasized the importance of directing surgical treatment to the underlying anatomic defect responsible for the lower eyelid malposition.

Dr Shaefer began his presentation with a discussion of involutional entropion, a problem that he feels is caused by a dehiscence of the lower eyelid retractors. His surgical repair is directed at this anatomic defect with a technique

Anatomy involved in eyelid malposition.



described by Jones and coworkers. The procedure is performed under local anesthesia with an incision in the skin at the lower border of the tarsus. Orbicularis oculi muscle is then incised and orbital septum is separated from the tarsus. A strip of skin and muscle is resected if redundant. A suture is placed through superior skin, lower tarsus, retractors, and inferior skin to reapproximate retractors to tarsus. After tying the suture, the patient is asked to look down. There should be a 3- to 4-mm downward excursion of the eyelid indicating restored function of the retractors. Several more sutures are placed and then left for 3 weeks to produce good scarring. With this procedure, support of the eyelid is restored without excision of normal eyelid tissue.

His treatment for cicatricial entropion is aimed at correcting the inward rotation of the eyelid margin. He suggests a traverse blepharotomy with the incision extending through the tarsus and conjunctiva. A mattress suture is then placed through the upper skin down to the tarsus and conjunctiva of the lower incision and back. This produces an outward rotation of the eyelid margin and a correction of the entropion.

A standard Kuhnt-Szymanowski procedure is recommended for repair of ectropion. This involves an incision 2-mm below the eyelid edge, with development of a skin flap as in a lower eyelid blepharoplasty. A wedge of tissue is then removed from the eyelid margin with careful closure of the defect. The skin flap is then pulled laterally and any excess tissue is removed prior to closure. For a medial ectropion, a horizontally directed diamond-shaped piece of tissue of conjunctiva and occasionally tarsus is removed with closure producing an inward rotation of the eyelid margin.

In cicatricial ectropion, the underlying problem involves scar tissue that is retracting the eyelid. Correction involves replacing this tissue with a flap or graft to relieve the retraction. A frost suture is often helpful in the early postoperative period to maintain a normal eyelid position.

Paralytic ectropion occurs with facial nerve paralysis. There are several methods of correction, which include gold weights, tendon tightening, and passive or dynamic slings, and the correct choice depends on many factors, including the age and health of the patient and etiology of the paralysis.

Last, Dr Shaefer discussed retraction of the lower eyelid in thyroid disease. This problem can be corrected either by recession of the lower eyelid retractors or using spacers. Material used for spacers includes fascia lata, sclera, or irradiated fascia. For placement of a spacer, the lid is approached from the inner surface and the tarsus is incised 1 to 2 mm above the lower border. The spacer is then placed and sutured to the eyelid retractors and tarsus in order to relieve the retraction of the lower eyelid.

In conclusion, he stated it was his goal to familiarize the audience with his technique for dealing with lower eyelid malpositions rather than an overview of all techniques available. He once again emphasized the importance of understanding the anatomy involved in eyelid malpositions (Figure).—DONNA J. MILLAY, MD, Seattle, Wash

In Other AMA Journals

AJDC

Age-Related Patterns of Violent Death, Cook County, Illinois, 1977 Through 1982
Katherine K. Christoffel, MD, MPH; Nora K. Anzinger, RN; David A. Merrill (*AJDC.* 1989;143:1403-1409)

Fetal Surgery in the 1990s
Mark I. Evans, MD; Arie Drugan, MD; Frank A. Manning, MD; Michael R. Harrison, MD (*AJDC.* 1989;143:1431-1436)

Regulation of Oxygen Concentration Delivered to Infants Via Nasal Cannulas
Nestor E. Vain, MD; Luis M. Prudent, MD; Deborah P. Stevens, RRT; Margaret M. Weeter, RRT; M. Jeffrey Maisels, MB, BCh (*AJDC.* 1989;143:1458-1460)

Prophylaxis of Recurrent Acute Otitis Media and Middle-Ear Effusion
Nicola Principi, MD; Paola Marchisio, MD; Emilia Massironi, MD; Rosa Maria Grasso, MD; Gianfranco Filiberti, MD (*AJDC.* 1989;143:1414-1418)

Study of Virus Isolation From Pharyngeal Swabs in Children With Varicella
Takao Ozaki, MD; Yoshiharu Matsui, MD; Yoshizo Asano, MD; Toshiomi Okuno, MD; Joichi Yamaishi, MD; Michiaki Takahashi, MD (*AJDC.* 1989;143:1448-1450)

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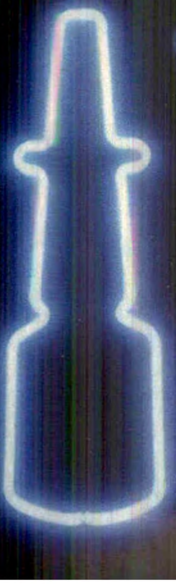

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brand of beclomethasone dipropionate, monohydrate **Nasal Spray, 0.042%***

Water-based formulation for greater patient comfort[1]

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Please see brief summary of prescribing information and references on following page.

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References: 1. Bronsky EA, Tarpay M, Tinkelman DA, Bush JK. A comparison of two dosing regimens of beclomethasone dipropionate aqueous nasal spray and flunisolide nasal spray in the treatment of acute seasonal rhinitis. *Immunol & Allerg Pract.* 1987;IX(5):165/11-170/16. **2.** Anderson P, Boyd G, Chatterjee SS, et al. A comparison of beclomethasone dipropionate aqueous nasal spray and beclomethasone dipropionate pressurized nasal spray in the management of seasonal rhinitis in adults and children. Clinical study report, 1985. **3.** Morrow-Brown H, Jackson FA, Pover GM. A comparison of beclomethasone dipropionate aqueous nasal spray and sodium cromoglycate nasal spray in the management of seasonal allergic rhinitis. *Allergol Immunopathol.* 1984;12:355-361.

VANCENASE* AQ

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Nasal Spray 0.042%*

FOR INTRANASAL USE ONLY

*calculated on the dried basis

INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate;* therefore, acute overdosage is unlikely.

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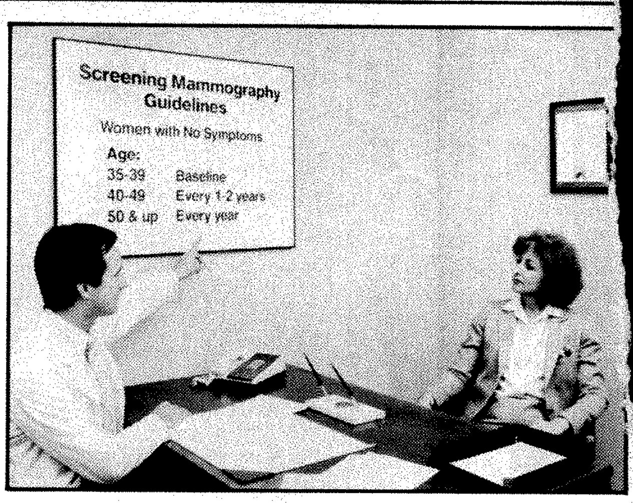

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Fretting Over Fragmentation

The Debate Continues

My commentary entitled "Fragmentation in General Surgery: the Case of Head and Neck Surgery,"[1] which appeared in the September 1989 issue of the *Archives of Surgery*, has engendered a vigorous response, both in this country and abroad. Much of the response has come from otolaryngologists who have interpreted my commentary as an attack on the specialty of otolaryngology. The commentaries by Drs Byron J. Bailey[2] and David Schuller[3] published in the December 1989 issue of the *Archives of Otolaryngology-Head and Neck Surgery* articulate their strong views in support of their specialty. It is certainly their right to use the pages of a respected and widely read journal to state their opinions. However, both Dr Bailey and Dr Schuller have taken some of my comments out of context. Dr Bailey, in particular feels that I have exhibited unprofessional and reprehensible conduct for having the temerity to disagree with some of the positions held by the specialty of otolaryngology. I, therefore, appreciate an opportunity to provide some additional clarification and background on the issues that have been raised. I wish to reiterate also that my opinions are based on my own experience and background in surgical education and that they do not necessarily reflect the thinking of any group or organization with which I am or have been associated.

The process of fragmentation in general surgery has been going on for many years, but it has now reached a point where the viability of the specialty is threatened. The issue of head and neck surgery is by no means the only one that is producing this fragmentation. My comments should not be construed to lay the blame for fragmentation at the feet of the specialty of otolaryngology. We general surgeons must share a great deal of the responsibility for the present state of affairs. In our zeal to maintain a broadly based education and experience for all general surgeons, we have not dealt well with the forces that have pushed medical and surgical practice to ever more narrow specialization. The future of general surgery is tied inevitably to the search for a solution to the problems engendered by fragmentation and specialization.

My comments should not be construed as an attack on the specialty of otolaryngology, nor should they be construed as a statement that otolaryngologists should not be active in the field of head and neck surgery. I make no claim for exclusivity in head and neck surgery for general surgeons. I do make a claim that general surgeons have historically been very active in the field of head and neck surgery, and that we continue to be active. The expansion of the involvement by otolaryngologists in head and neck surgery is felt by many general surgeons to have developed at the expense of general surgery. This is not an accusation. It is merely a statement that this perception is widely held in general surgical circles. I do agree with Dr Bailey that accurate data on who is actually performing head and neck surgery throughout the country are difficult if not impossible to obtain. The experience in the academic medical centers may or may not be reflective of the country as a whole. In the absence of a reliable database, it is not useful to argue about which specialty exerts primacy over the other. Let us simply leave it that both specialties have a significant interest and involvement in head and neck surgery, and that this interest and involvement should be accepted and recognized.

Let us also accept and recognize that neither specialty makes any explicit claim of exclusivity in the area of head and neck surgery. However, one of the most troublesome issues has been the use of the hyphenated term *otolaryngology-head and neck surgery* by the specialty of otolaryngology. This term clearly carries with it intimations of exclusivity and implies an identity between those two disciplines. We may debate about whether all otolaryngologists are head and neck surgeons, but the fact that not all head and neck surgeons are otolaryngologists is beyond question. This is part of the reason that the American Board of Medical Specialties has repeatedly denied a request to change the name of the American Board of Otolaryngology. It is also not beyond the realm of possibility that we could be faced in the future with a request to drop the term *otolaryngology* altogether on the basis of the same arguments that have already been advanced, namely that the term *otolaryngology* is difficult to understand and does not reflect the breadth of the specialty. As long as the specialty of otolaryngology persists in using the hyphenated term *otolaryngology-head and neck surgery* to describe itself, there will continue to be conflict. It seems to me that it should be possible to find a name that would accurately describe the specialty without the implication that head and neck surgery and otolaryngology are identical.

I have also been interpreted as being opposed to the development of specialization and, in particular, as being opposed to specialization in head and neck surgery. I am not opposed to either one of these. My commentary was written in part in reaction to new proposals for changes in the special requirements for residency training in otolaryngology. These requirements were so broadly written as to put every organ system and structure that was either located in, passed through, or was connected to the head and neck under the purview of the specialty of otolaryngology. Everything between the cranium and the clavicles (or, as some wags have put it, from the dura to the pleura) was considered to be a part of the specialty of otolaryngology. I am not specifically opposed to regional specialization, but realistic limits have to be placed on it. In a region as complex as the head and neck, it is unrealistic to think that any surgeon could become expert in dealing with all of the diseases and injuries that could happen to all of the structures and organ systems in the head and neck. Certainly such expertise would be impossible in the absence of a multidisciplinary and comprehensive training program. The meeting to which Dr Schuller refers, among the chairmen of the residency review committees for otolaryngology, general surgery, plastic surgery and neurological surgery, was actually quite constructive. Some modifications were made in the special requirements for otolaryngology subsequent to my submission of the commentary for publication in the *Archives of Surgery*, and a set of revised requirements has recently been approved by the Accreditation Council for Graduate Medical Education.

My discussion about preparatory training for head and neck surgery was not at all meant to imply that otolaryngologists are unqualified to practice head and neck surgery. Some head and neck surgical procedures are extremely complex, and as our patients become older and sicker, the patients themselves are becoming more complex. Preparation for this type of surgery should, in my view, be based on a broad exposure to the basic principles of surgery, surgical pathophysiology, and surgical care. As Hayes Martin[4] said in the preface to his classic textbook, *Surgery of Head and Neck Tumors*, "I am convinced that the wide range of head and neck surgery can be performed successfully only by those who have a broad basic training in general surgery." Surgeons intending to specialize in head and neck surgery should have a much broader experience in general surgery than the 1-year minimum that is currently required by the specialty of otolaryngology.

My comment about interventionists, or "halfway surgeons," clearly did not refer to otolaryngologists or any other group of recognized surgical specialists. It was directed at those individuals who may become very proficient in a narrow area of specialization based on technological advances but who are not either capable of or willing to assume responsibility for dealing with the consequences of their interventions. The remark was also directed at those individuals who practice beyond the limits of their specialties without adequate training and experience. Specialization has produced many benefits, but the danger is that it can produce physicians who are too narrowly focused and who become "merchant technicians" instead of true professionals. As Francis Moore[5] has indicated, "The fundamental act of medical care is assumption of responsibility." This responsibility can be shared to a certain extent, but it does not start with the performance of a technical procedure, nor does it end there. The responsibility must have sufficient continuity so that the principles of proper patient care can be maintained, and it cannot be abrogated. It would be a sad commentary on our profession if we allowed the pressures for increasing specialization to interfere with the ability of surgeons to assume the responsibility of continuing care for their patients.

Finally, there is no question that we are dealing in this set of issues with deeply held convictions and emotions on both sides. There are still some significant areas of difference, about which discussions no doubt will continue. I fully agree with Dr Bailey's call for mutual understanding and cooperation. I regret that Dr Bailey has chosen to reduce his argument largely to an ad hominem diatribe, a process that Dr Bailey[6] himself has decried in the past. I do not believe that I did any of the things of which Dr Bailey accuses me, and I offer no apologies for my published commentary. It must be remembered that cooperation is a two-way street, and there can be no progress toward cooperation if we continuously shout monologues at each other. Cooperation should be based on a mutual understanding of concerns and a mutual willingness to solve the problems. This process can only be carried out on a plane of rational and civilized discourse, and if that can be achieved, perhaps we can continue to make some progress.

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Editorial

Expanding Interspecialty Cooperation

I want to thank Dr Friedmann for taking the time to clarify some of the contentions he raised in his original commentary that appeared in the *Archives of Surgery*.[1] I feel certain he realizes that when a leader in the field of surgical education chooses to publish controversial ideas in a prestigious journal that a reasonable expectation is that these views will be challenged and answered. Objective review of my editorial response[2] will show that it was not an ad hominem diatribe. There was no personal attack on Dr Friedmann's character, which I believe to be entirely above reproach on the basis of his excellent reputation. The focus of the responses in the ARCHIVES by Dr Schuller,[3] Dr Alford,[4] and myself were Dr Friedmann's contentions, particularly those that seemed to us to be derogatory or misleading. My responding editorial does not qualify as a diatribe, as it was relatively brief and specifically lacking in bitterness, abusiveness, and ironical or satirical criticism. There was no accusation that Dr Friedmann was guilty of "reprehensible behavior."

The two commentary pieces by Friedmann are worth our time in terms of careful analysis, as they give us an interesting account of how we appear to someone in the leadership ranks of another specialty. Like the editorial in the *American College of Surgeons Bulletin* by Dr M. J. Jurkiewicz,[5] they tend to paint us in a negative light and seem to allege that we are somehow less prepared to deal with head and neck surgery than are general surgeons and plastic surgeons, who presumably are not fragments, but are part of the greater whole. There isn't anything especially remarkable or new about these essays, other than the prominence of the journals in which they appear and the eminence of the positions held by the authors. I doubt that the readers of our journals have taken either of these published articles as welcome steps toward greater interspecialty cooperation.

I imagine that by now most of our readers have had about enough of this exchange (it is not a debate) for the moment. It would not be worthwhile to rehash each phrase and, more to the point, it would be counterproductive in our effort to move beyond interspecialty conflict and toward interspecialty cooperation. We realize that most otolaryngologists and general surgeons enjoy good professional relationships in their local communities and we have no wish to injure those through our editorial exchanges. We acknowledge that Dr Friedmann is an articulate and effective spokesman for his specialty and move on in search of greater understanding of some of these fundamental issues.

What avenues are open to us that might lead to the building of closer ties with other specialties, rather than to escalating divisiveness on the national level? I believe that we should continue to work diligently within such organizations as the American Medical Association and the American College of Surgeons to build positive and productive coalitions with other specialties. Improving educational resources and upgrading training programs are common goals of such organizations, and many of these activities carry a positive, collegial atmosphere. By working more closely together we can increase the emphasis on the growing list of common problems and mutual goals among all surgeons, rather than placing an unrealistic emphasis on our differences and our quarrels. By working together to promote more effective programs for raising the standards of surgical care in the United States, we will be addressing real problems and working toward important solutions. I believe that much could be accomplished if we would exert a joint effort to achieve expanded funding for research in surgical disciplines. Most of us recognize that surgical research, in general, is lagging severely, and if it is not strengthened, the surgical practice of tomorrow will be more limited than we would wish. There is much to be done in working with governmental entities to develop more effective programs to increase the access to high quality surgical care for the 37 million indigent and underserved/underinsured citizens of our country. Our patients will be better served if we can put this arguing behind us and focus our attention on more important matters during the 1990s.

Byron J. Bailey, MD
Chief Editor

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The Incidence of Aminoglycoside Antibiotic-Induced Hearing Loss

Robert E. Brummett, PhD, Robert B. Morrison, MS

• The definition of ototoxicity in most clinical studies of aminoglycoside antibiotics is an increase in pure-tone threshold from a baseline audiogram ≥15 dB at two or more frequencies, or ≥20 dB at one or more frequencies. In this study, test-retest auditory threshold differences of this magnitude were found in a group of 20 normal volunteers who were not taking any known ototoxic drugs. Depending on which of the two criteria for ototoxicity are used, these data represent a 20% or 33% incidence of ototoxicity. We believe that many of the audiometric changes reported to represent aminoglycoside antibiotic ototoxicity may actually represent the normal test-retest variability of pure-tone audiometry. If this is true, the reported incidence of hearing loss due to aminoglycoside antibiotics may be exaggerated.

***(Arch Otolaryngol Head Neck Surg.* 1990;116:406-410)**

Aminoglycoside antibiotics have been shown to produce ototoxicity in both humans and experimental animals.[1-3] In 1945, the first report of the clinical efficacy of streptomycin, the first aminoglycoside antibiotic, described hearing loss in some patients.[4] However, the incidence of hearing loss resulting from aminoglycoside antibiotics in man remains controversial.

This controversy exists because of the discrepancies between the clinical observation that very few patients receiving aminoglycoside antibiotics complain of a hearing loss,[5] and the reported incidence of aminoglycoside antibiotic-induced ototoxicity of up to 82% in studies in which auditory thresholds are monitored.[6] It is our belief that one of the fundamental reasons for this discrepancy is the definition of ototoxicity in terms of auditory threshold changes used in clinical investigations. The same problem has troubled investigators trying to determine a definition for test-retest difference that would be suitable for noise-induced hearing loss and hearing conservation programs.[7,8] As an illustration of this problem, Table 1 contains the 95% confidence intervals for the test-retest variability of pure-tone thresholds published by some of these investigators.[9-13]

Two criteria are generally used for identifying hearing loss in most aminoglycoside antibiotic ototoxicity studies: an increase in pure-tone threshold of ≥15 dB at any two or more frequencies[14] or ≥20 dB at any one or more frequencies.[15] It is reasoned that since pure-tone thresholds are obtained using 5-dB steps, there would be a minimum measurement error of ±5 dB. Therefore, if a baseline threshold had a −5-dB error and a subsequent threshold had a +5-dB error, the difference between the two would be 10 dB. Therefore, a 10-dB change in threshold between two audiograms could be attributed to normal variability.

The next largest change would include an additional 5 dB, making 15 dB the smallest meaningful change greater than the measurement error. It is known that pure-tone threshold changes of 15 dB or greater occur in normal humans.[7,8] If these individuals were participating in an aminoglycoside antibiotic ototoxicity study, these changes would be considered to represent ototoxicity. In general, most aminoglycoside antibiotic ototoxicity studies do not contain a control (placebo-treated group) or a comparison group (non-aminoglycoside-treated group) for comparison with the aminoglycoside-treated group. However, four aminoglycoside antibiotic ototoxicity studies that did include comparison groups are summarized below.

Davey et al[16] published data on two groups of subjects they considered to

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be comparison groups for aminoglycoside antibiotic ototoxicity studies. The first group consisted of 24 normal volunteers who were tested on 2 consecutive days. Only one subject had a change in threshold greater than 10 dB between the two tests (a 15-dB increase in threshold at 8 kHz). The second group consisted of 27 patients who were hospitalized but did not receive aminoglycoside antibiotics. Two sets of pure-tone thresholds were obtained with an intertest interval of 3 to 5 days. Increases in thresholds of 20 to 60 dB were recorded at one or more frequencies in 15 subjects, and in 10 subjects the thresholds had decreased.

In another study, Davey et al[17] investigated the variability of audiograms collected from another comparison group that consisted of 27 inpatients who were not treated with any known ototoxic drugs. Fifteen patients had a change in pure-tone thresholds between 20 and 35 dB at one or more frequencies during their stay. Five of these changes represented an apparent improvement, and in 10 cases hearing appeared to deteriorate. The changes were temporary in 11 of the 15 patients and permanent in 4. All cases of hearing improvement were temporary.

In 1986, Worning et al[8] reported the results of a prospective, double-blind, placebo-controlled study of 141 patients who received methicillin and netilmicin before reconstructive vascular surgery. Two patients had a moderate hearing loss after treatment; both had received the placebo. No criteria for the hearing loss were stated except that "If ototoxicity was suspected the patient was referred to the Otology Department, which monitored eighth cranial nerve function by pure-tone audiometry, electronystagmography when possible, and by clinical assessment of signs and symptoms."

In 1984, Smith et al[19] studied patients treated with cefotaxime compared with those treated with nafcillin plus tobramycin. These investigators reported that 13% of the patients in the cefotaxime-treated group and only 7.4% of the patients treated with nafcillin plus tobramycin met their ≥15-dB increase in threshold at any frequency criteria for ototoxicity. Smith[20] investigated ototoxicity in normal volunteers treated with gentamicin, netilmicin, or placebo. No patients in any treatment group met their unstated criteria for ototoxicity.

It appears that pure-tone thresholds can be variable enough to be erroneously interpreted as drug-induced ototoxicity. If this is true, then the reported incidence of aminoglycoside antibiotic-induced ototoxicity may be greatly exaggerated.

Table 1.—95% Confidence Intervals for Test-Retest Variability of Pure-Tone Thresholds*

Frequency, Hz	Confidence Interval, dB Witting and Hughson,[9] 1940†	 Atherley and Dingwall-Fordyce,[10] 1963‡	 Pelmear and Hughes,[11] 1974§	 Bryan et al,[12] 1965
125	9	...	...	17
250	9	...	...	17
500	8	10	13	11
1000	6	10	11	11
2000	8	7.5	9	14
3000	...	7.5	11	...
4000	8	12.5	13	20
6000	...	12.5	17	17
8000	9	15	...	20

*Adapted from Bryan,[13] 1976.
†297 audiograms on 17 pathologic ears.
‡Rounded to the next highest 2.5 dB.
§Thresholds were determined using Bekesy traces; all other studies used manual audiometry.

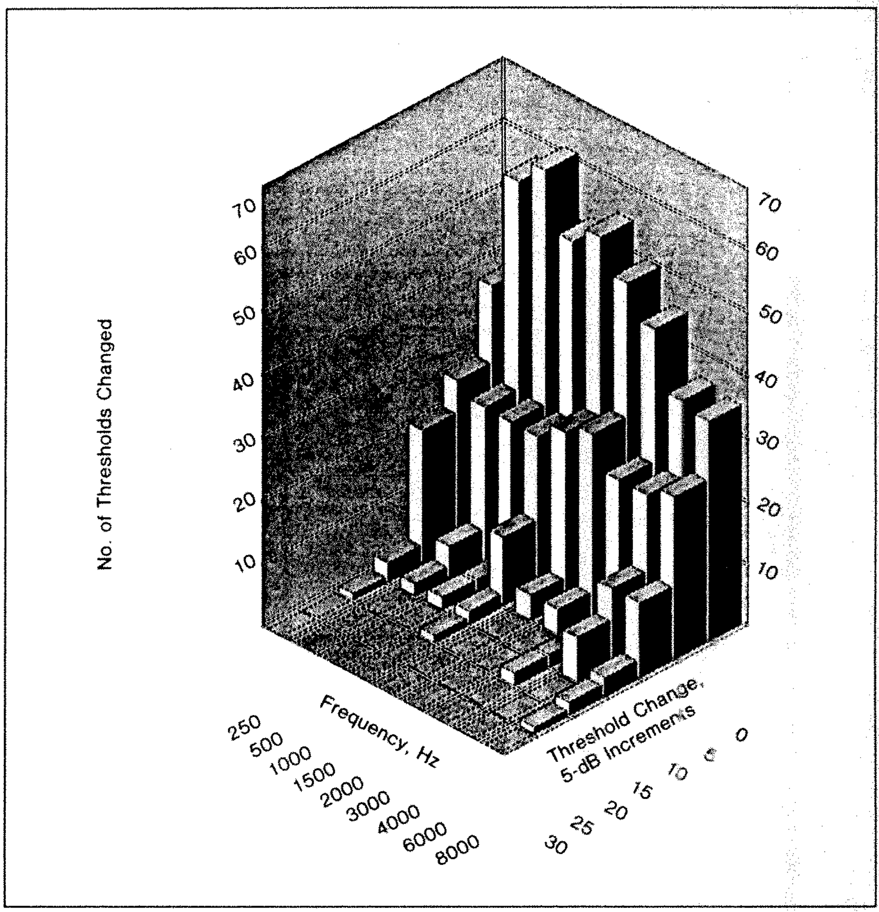

Fig 1.—Test-retest differences in which the auditory threshold improved.

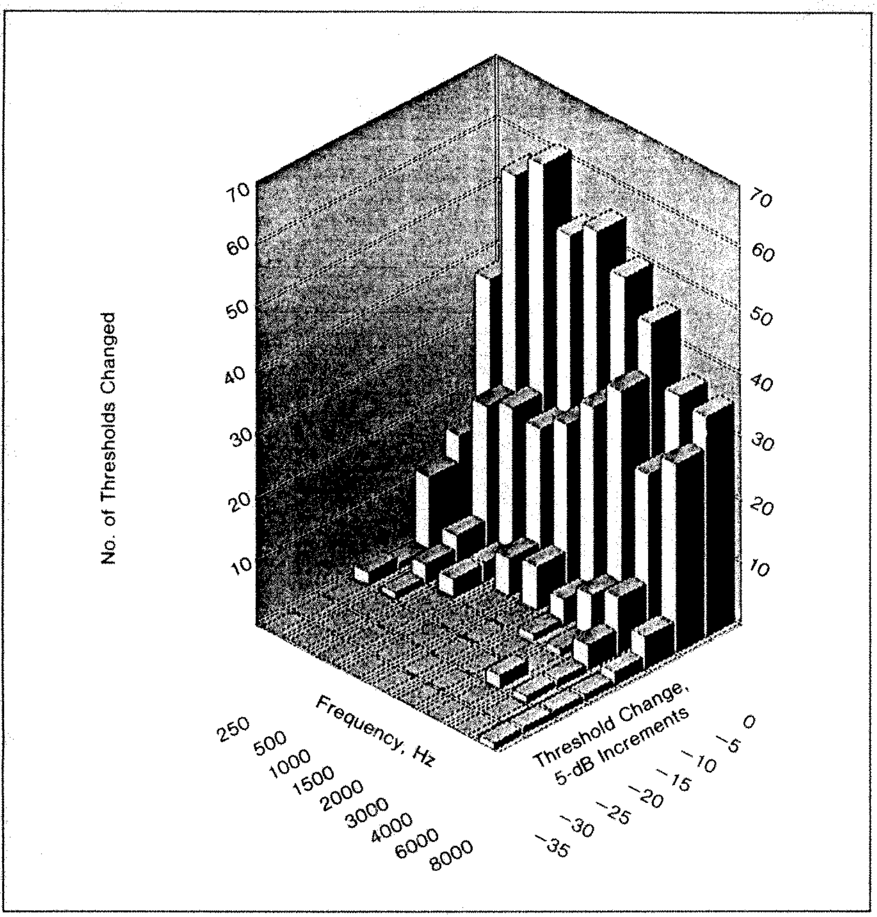

Fig 2.—Test-retest differences in which the auditory threshold worsened.

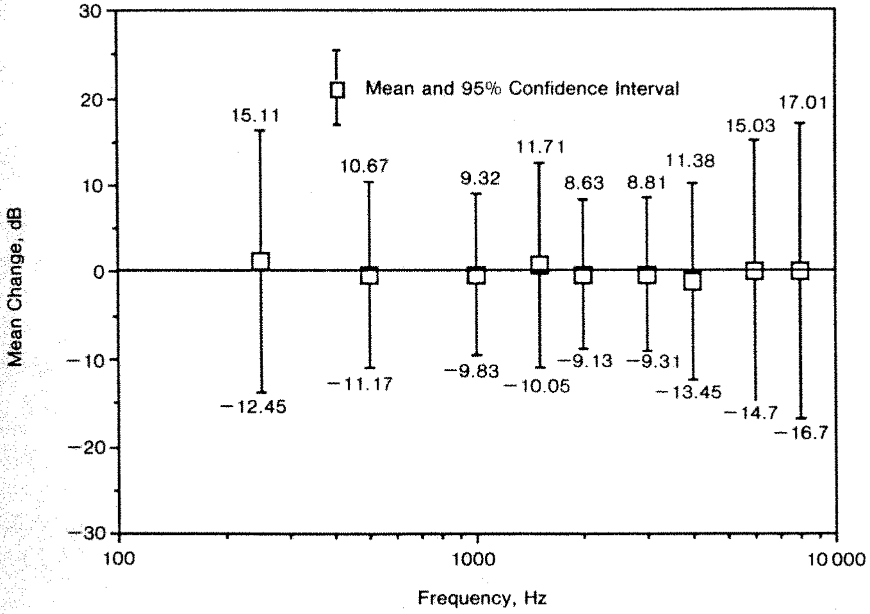

Fig 3.—Ninety-five percent confidence intervals of the test-retest auditory threshold differences.

This study was designed to determine the variability of auditory threshold changes that occur in a test-retest situation designed to simulate an ototoxicity study. Pure-tone air conduction audiograms were collected from 20 normal subjects receiving no known ototoxins. Three audiograms were collected in each case, simulating a baseline before aminoglycoside antibiotic therapy started, at the end of 1 week of therapy, and 1 week following therapy.

SUBJECTS AND METHODS

Subjects

The subjects were healthy volunteers between ages 25 and 63 years solicited from the staff of the Oregon Health Sciences University, Portland. There were 6 men and 14 women. No attempt was made to screen patients with preexisting sensorineural hearing loss. Subjects with conductive hearing loss or evidence of active middle ear disease were excluded. All subjects had measurable hearing at all test frequencies.

Methods

All auditory threshold determinations were made in a double-walled, sound-attenuated audiometric chamber (Industrial Acoustics Co, Bronx, NY) using an audiometer (GS 1701, Grason Stadler, Littleton, Mass). The audiometer was calibrated to American National Standards Institute standards[21] just before beginning the study, at the midpoint, and after the last subject had been tested. No changes in the output sound pressure levels were observed. To exclude the possibility that output changes occurred during the "warm-up" period, the audiometer was calibrated immediately after being turned on and again after remaining on for 30 minutes. No differences between the two measurements were observed, and no systematic errors in the data were found that would suggest that the calibration had changed at any time during the experiment. Thresholds were determined using American Speech and Hearing Association guidelines[22] at the standard and half-octave audiometric frequencies (0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz). The test tones were presented using TDH-39 headphones in MX-41 AR cushions (Telephonics Corp, Huntington, NY).

Subjects were tested on three occasions, each separated by at least 1 week. All testing was performed by the same audiologist. To control for observer bias, the previous threshold data were unavailable to the tester at the time of each subsequent test. Data entry and analysis did not begin until all audiograms had been collected. The test data were entered into a computer (Macin-

Table 2.—Auditory Threshold Changes Found in Subjects Meeting Currently Accepted Criteria for Ototoxicity

	Threshold Change, dB					Met Criteria for Ototoxicity	
Subject No.	End of Treatment	Follow-up	Frequency, (kHz)	Ear	Onset	≥15 dB*	≥20 dB†
1	−25	−20	8	L	Early	No	Yes
5	−15	−20	0.5	R	Early	No	Yes
8	−20	−25	6	R	Early	Yes	Yes
	...	−15	1	R	Delayed	...	...
	...	−15	4	R	Delayed	...	...
	...	−15	8	R	Delayed	...	...
14	−15	−15	0.25	L	Early	Yes	No
	...	−15	6	L	Delayed	...	...
15	...	−15	6	L	Delayed	Yes	No
	...	−15	8	L	Delayed	...	...
17	−15	−15	0.5	R	Early	Yes	Yes
	−25	−25	4	R	Early	...	...
	−15	−15	1	R	Early	...	...
	...	−15	3	L	Delayed	...	...
18	−30	−35	8	R	Early	No	Yes

*At two or more frequencies.

†At one or more frequencies.

tosh II, Apple Computer Co, Cupertino, Calif) and statistical analysis was performed using Stat View II.

RESULTS

A total of 1080 pure-tone air conduction thresholds were obtained. Nine frequencies were tested in both ears on three different occasions. Threshold differences were calculated between the first test (baseline), the second test (theoretical end of treatment), and the third test (theoretical 1-week follow-up). Differences between the first and second test results represent early- or immediate-onset changes; and differences between the second and third or the first and third test results represent delayed changes.

Test-retest differences were separated into two groups: those in which the auditory threshold improved and those in which the auditory threshold worsened. The threshold improvements are shown in Fig 1; thresholds in which hearing worsened are shown in Fig 2. While most of the test-retest differences were small (from 0 to 10 dB), some were considerably greater. There were 26 differences of 15 dB or more in which the threshold improved and 27 in which the threshold worsened. The 95% confidence intervals of the test-retest threshold differences at all nine test frequencies are shown in Fig 3. The number of individuals who had increases in their thresholds from baseline that would fit the criteria of ototoxicity of ≥ 20 dB at any frequency or ≥15 dB at two or more frequencies is shown in Table 2.

Four subjects had threshold increases of ≥20 dB at one frequency for an ototoxicity incidence of 20%, and six had a ≥15 dB increase at two or more frequencies for a 33% ototoxicity incidence. There were eight cases of early changes, none of which recovered, and six cases of delayed change. The delayed changes were not checked for recovery. In a similiar manner, four individuals (20%) had test-retest threshold differences in which the threshold improved by ≥20 dB at one or more frequencies, and six individuals (33%) had improvements of ≥15 dB at two or more frequencies. Subjects like these, with thresholds that appear to improve, are almost never discussed in ototoxicity studies.

COMMENT

The majority of the threshold changes measured in this study fell within the range of no meaningful change (ie, ≤10 dB). The 95% confidence intervals of our data are similiar to those of previous studies. Nevertheless, differences greater than 10 dB were observed. Using the two currently accepted criteria for auditory threshold changes representing aminoglycoside antibiotic-induced ototoxicity, the incidence of "ototoxicity" in the present study ranged from 20% to 33%. Since the subjects were not receiving any aminoglycoside antibiotics or other known ototoxic agents, the reasons for these changes are unknown. Among the possibilities are the known sources of measurement error for pure-tone audiometry. The most likely source of measurement error is inaccurate headphone placement.[23] Great care was used to accurately place the headphones in accordance with American Speech and Hearing Association guidelines, and subjects were instructed not to move the headphones once in place.

There are many variables that affect auditory threshold measurements. A partial listing includes: sound pressure level and frequency output changes of the audiometer within American National Standards Institute standards[24]; fluctuating conductive hearing losses resulting from allergies, middle ear and atmospheric pressure changes, collapsed external auditory canals, the common cold, and other sources; use of drugs such as aspirin; attentiveness, learning effects and motivation of the test subjects, and noise-induced temporary threshold shifts; extraneous noises in the test equipment; and changes in the subjects' response criteria.[23,25-32] It is possible that some or all of the above variables may account for the observed variability in the present study. However, some or even all of the present findings may represent true changes in auditory thresholds.

We believe many of the audiometric threshold changes reported to represent aminoglycoside antibiotic ototoxicity may actually represent normal variation in audiometric threshold measurements found in normal individuals. Aminoglycoside antibiotic-induced hearing loss remains a serious complication, but the reported incidence of hearing loss due to this class of drugs may be exaggerated.

Because the aminoglycoside antibiotics begin their ototoxic effects by damaging cochlear function that involves hearing very-high-frequency sounds,[33] we recommend that before any hearing loss is assumed to represent aminoglycoside antibiotic ototoxicity, it should be predominantly high-frequency (>8 kHz) and be ≥20 dB. This would not eliminate the possibility that measured changes do not represent ototoxicity, but it would surely minimize the risk of such an error. The available high-frequency hearing test equipment requires too much patient cooperation, and it takes too long to conduct the test to be suitable to test very sick patients. We are currently developing a system that can be used to screen high-frequency hearing very quickly in sick individuals.

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Cochlear Microcirculation

Effect of Adrenergic Agonists on Arteriole Diameter

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• We used intravital fluorescent microscopy coupled with computerized video image processing to examine the cochlear microvasculature. In Mongolian gerbils the bulla was opened ventrally and a small window was made in the second turn of the cochlea. After fluorescein isothiocyanate–dextran administration, the radiating arterioles were video-recorded under ×675 magnification. Computer determinations of arteriolar response to norepinephrine bitartrate (mixed α_1/α_2 agonist), phenylephrine hydrochloride (α_1 agonist), and UK 14 304 tartrate (α_2 agonist) were made at multiple dose levels over time. Findings were consistent with arteriolar constriction in response to α-adrenergic stimulation. The presence of α_1 and α_2 receptors was established, and a predominance of α_2 receptors in the cochlea was suggested.

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Sudden sensorineural hearing loss is a clinical disorder that represents a frustrating diagnostic and treatment dilemma for the practitioner. Microcirculatory insufficiency in the form of vascular occlusion from embolus, hemorrhage, or vasospasm is a possible cause. Hyperviscosity syndromes as well as the microangiopathies associated with diabetes mellitus and hypertension are also implicated. In addition, infection and loss of anatomic integrity are substantial etiologic contributors, with viral cochleitis believed to be the single most common cause of sudden hearing loss.[1]

Treatment is typically in the form of a "shotgun" regimen[2] and is directed at the suspected cause based on a clinical judgment. The drugs that are used have an uncertain efficacy in a heterogeneous population and can have a spontaneous cure rate as high as 70%.[3] A basic understanding of cochlear microcirculatory mechanisms is essential to establish a foundation that will permit the formulation of rational therapeutic approaches. The role of the autonomic nervous system in the regulation of inner ear microcirculation has yet to be defined. Our goal was to determine whether cochlear microcirculation possesses postjunctional α_1- and α_2-adrenergic receptors and to determine if they participate in the regulation of cochlear blood flow.

Spoendlin[4] demonstrated by histochemical methods direct adrenergic innervation of inner ear arteries to the level of the labyrinthine artery and its immediate modiolar branches. Recent work in our laboratory has demonstrated, by histochemical techniques, adrenergic innervation of the proximal portion of radiating arterioles. It remains to be determined whether these microvessels are controlled by this sympathetic innervation.

Specific receptors for different neurohumoral substances, including catecholamines, are believed to exist on vascular smooth muscle of peripheral arterioles and venules.[5] There are two main types of receptors: α receptors, which cause vasoconstriction, and β receptors, which cause vasodilation. The actions of norepinephrine and epinephrine, for example, depend to some extent on the kind of receptors present in different tissues and their respective affinities for norepinephrine and epinephrine.

α-Adrenoreceptors are subclassified into postsynaptic α_1 and α_2 receptors and presynaptic α_2 receptors on adrenergic nerve varicosities. Postsynaptic α_1 and α_2 receptors mediate constriction, while presynaptic α_2 receptors act by negative feedback to inhibit neurotransmitter release.[6] Whether α_1 and α_2 adrenoceptors on vascular smooth muscle subserve unique physiologic functions is unknown.

The distribution of α_1- and α_2-adrenergic receptors has been partially identified in the general circulation based on indirect in vivo studies and direct in vitro examination of large arteries and veins.[7,8] Recent studies suggest that postsynaptic α_2 adrenoreceptors are most evident on small than on large arteries in heart[9] and brain.[10] Using selective agonists and antagonists, Faber[11] documented in microcirculatory studies that smooth muscle of large arterioles and venules in skeletal muscle have both α_1 and α_2 adrenoreceptors. α_1 Receptors appear to be more dominant on the large arterioles and α_2 adrenoreceptors more dominant on the large venules. In distinction, small precapillary arterioles have predominantly α_2 receptors. The significance of this selective distribution of postjunctional α receptor subtypes is unclear.

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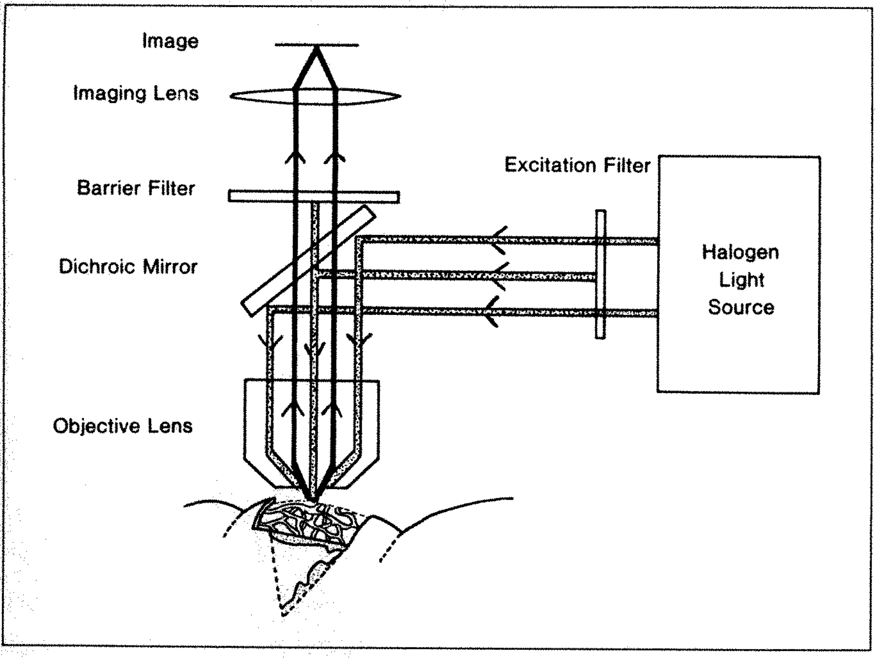

Fig 1.—Schematic diagram of intravital fluorescent microscope viewing the stria vascularis through a bony window in the second turn of the cochlea.

MATERIALS AND METHODS

Fifteen healthy adult Mongolian gerbils weighing between 50 and 80 g were anesthetized with a combination of alpha chloralose (70 mg/kg) and urethan (425 mg/kg). A right ventrolateral neck dissection was performed followed by tube tracheostomy to ensure free breathing. The ipsilateral carotid artery was cannulated in a retrograde fashion for continuous heart rate, blood pressure measurement, and slow fluorescein isothiocyanate-dextran administration (30 mg per 100 g) as well as constant infusion (rate of total infusate, 14.0 μL/min per 100 g) of phosphate-buffered saline. Body temperature was maintained at 38°C.

The technique for intravital fluorescent microscopy is described in detail elsewhere.[12] After the neck dissection, the bulla, a hollow, ventrally located skull base structure that houses the cochlea, was opened. The cochlea, which is freely visible and encased only in a thin, closely adherent, bony shell, was examined and the second turn identified. Next, medial to the cochlear base, the bone was thinned until the anterior inferior cerebellar artery (AICA) was exposed to the point at which it branches into the labyrinthine, common cochlear, and vestibular arteries. The bony wall of the cochlea was gradually thinned over the area of the stria vascularis at the second turn, creating a small window. Care was taken not to injure the subjacent cochlear ligament. To prevent tissue drying, the surface of the tissue was intermittently superfused with phosphate-buffered saline at 37°C. Fluorescein isothiocyanate-dextran was slowly infused at a dosage of 30 mg per 100 g of body weight to permit blood vessel visualization. The window was observed with a Zeiss fluorescence microscope with a 450- to 510-nm excitation filter, a dichroic mirror with a 510-nm suppression filter, a ×40 long working distance objective, and a 50-W mercury vapor light source (Fig 1). Images were captured with a silicon-intensified target video camera, viewed on a high-resolution monitor, and recorded by a high-resolution video recorder for later analysis.

The study was designed with five animals per group, with each group receiving one of the following drugs: norepinephrine bitartrate, a potent mixed α and β agonist; phenylephrine hydrochloride, a selective α_1-adrenergic agonist; and UK 14 304 tartrate, a selective α_2 agonist.[13] The dosage ranges for all the drugs were determined in pilot experiments. They were administered as infusions to eliminate the myogenic contractile response to bolus administration. Doses were selected that produced regional vascular responses without affecting the heart rate and blood pressure, permitting comparisons between different drugs without the contamination of systemic effects. The concentrations were as follows: norepinephrine bitartrate, 0.01, 0.1, and 1.0 μg/kg per minute; phenylephrine hydrochloride, 0.01 and 0.1 μg/kg per minute; and UK 14 304 tartrate, 0.01, 0.1, and 1.0 μg/kg per minute. Each drug was administered over a 20-minute test interval by an infusion apparatus through the retrograde cannulated right carotid artery at very low infusion rates as part of a constant infusion of pH-balanced (7.2) ascorbated phosphate-buffered normal saline. The only variable was the presence and concentration of the investigated drug. The vehicle (ascorbated phosphate-buffered saline) infusion rate (14.0 μg/L/min per 100 g of body weight) was chosen to maintain euvolemia. Drug infusates were determined based on the volume fraction of drug required from a stock-drug solution of known concentration that had to be part of the total volume of phosphate-buffered saline that was to be infused over the experimental time period (ie, 8.4 μL/min for a 60-g gerbil for 20 minutes). Catecholamine stock solutions were prepared on a daily basis and kept at 40°C in the dark; drugs were warmed to body temperature prior to administration. Ascorbate was added to the solutions at a concentration of 1×10^{-6} mol/L to prevent oxidation of the catecholamines. This concentration has not been found to have a significant effect on vascular smooth muscle.[11]

Cochlear preparations were considered adequate for study if (1) heart rate and blood pressure remained stable; (2) there was no evidence of spiral ligament injury; (3) collateral microcirculation displayed brisk, continuous flow; and (4) a total experimental time period of 3 hours was not exceeded. Based on these criteria, five experiments were eliminated because of cochlear ligament injury during dissection (two each from the phenylephrine and norepinephrine groups and one from the UK 14 304 group). Phenylephrine dosages above 0.1 μg/kg per minute were found to increase heart rate and blood pressure significantly and were not included in this series.

Data were collected routinely in the following manner. The first 10 minutes of each experiment established the baseline data for heart rate, blood pressure, and arteriole diameter. The next 20 minutes was the administration period for the first dose of 0.1 μg/kg per minute, followed by 20 minutes of pH-corrected phosphate-buffered saline (ascorbated) to reestablish baseline, followed by dosage of 1.0 μg/kg per minute for 20 minutes. The same pattern was maintained in the experiments in which three doses were used. The diameter of the AICA was also determined for the first 3 minutes of the initial and all subsequent baseline (control) periods. This allowed detection of any upstream arterial effects that may be important in evaluating the downstream cochlear microvasculature responses.

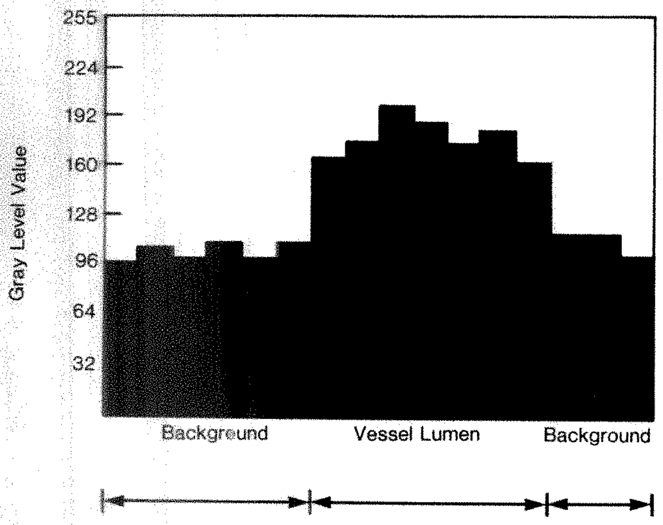

Fig 2.—Histogram of the cross-sectional gray scale distribution of a radiating arteriole (ranging from 0 representing black to 255 representing white).

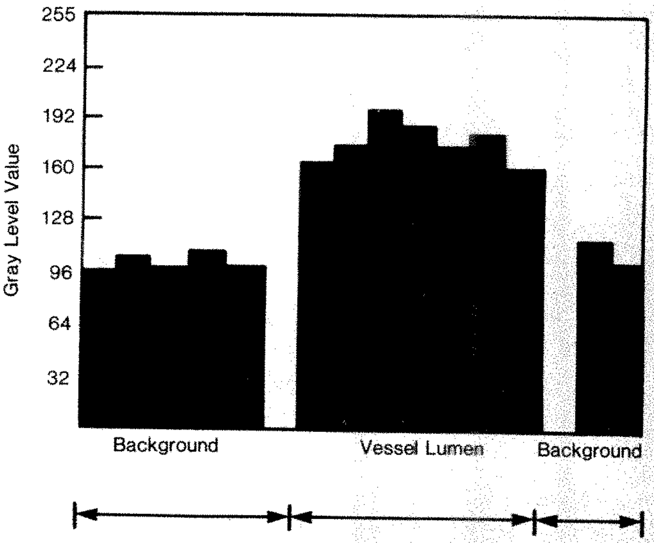

Fig 3.—The lower index value (vessel edge) was set to an arbitrary value for easy computer recognition and visual detection.

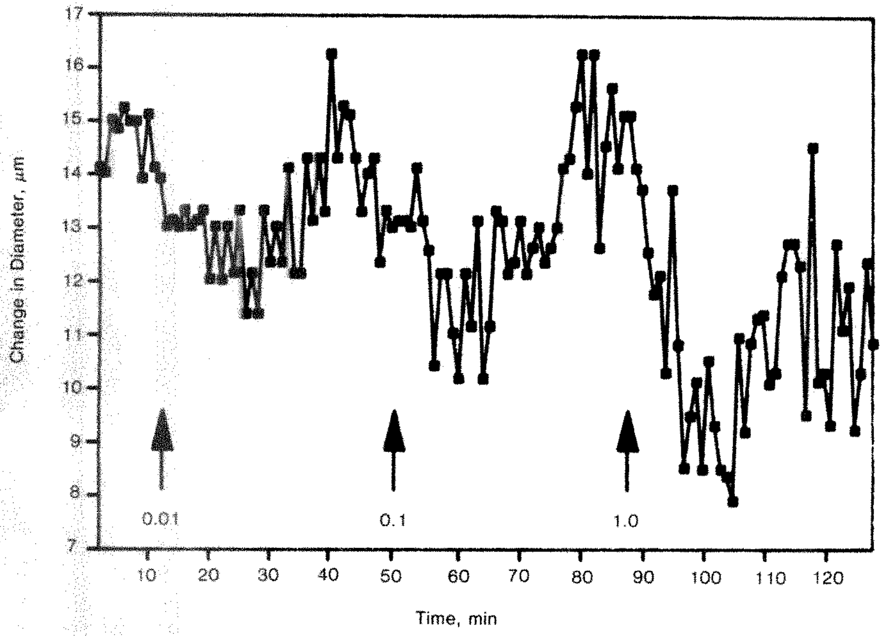

Fig 4.—Norepinephrine raw data curve showing minute by minute changes in diameter of one arteriole (squares) in response to drug infusion (in micrograms per kilogram per minute) and intervening baseline periods.

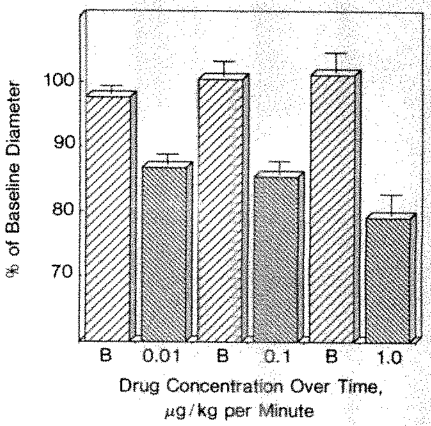

Fig 5.—The reaction of radiating arterioles to norepinephrine administration. Bars labeled "B" indicate baseline diameters between doses. The other three bars represent the dosage of norepinephrine infused and the percent of decrease from baseline arteriole diameter. The time span is 120 minutes, with the baseline period being 10 minutes long and the subsequent intervals each being 20 minutes.

Analysis was performed using a computer equipped with a dual-scanning real-time image processor. Videotapes were analyzed using software with image analysis (including measurement function) and image enhancement capabilities. This technique is discussed elsewhere (V.N.C., Garrett CG, R.J.T. et al, in preparation, 1990); briefly, vessel diameter measurements were obtained once per minute at a final magnification of ×675. Vessel diameter was measured by placing a computer-generated perpendicular line across the image of the vessel of interest, including the immediate extra-vessel background. A gray-scale distribution was generated across the pixels of the perpendicular line that displayed the color index value at each pixel (ranging from 0 representing black to 255 representing white) (Fig 2). The luminal boundary was detected by identifying the point at which there was a large change in the color index values between adjacent pixels. This represented the boundary of the bright intraluminal fluorescent plasma and the dark vessel wall. The lower index value (vessel edge) was set to an arbitrary value for easy computer recognition and visual detection (Fig 3). The image was then colorized using an exponential true color palette.

Vessel segments were chosen by the observer and were characterized as capillaries, arterioles, and venules. This was achieved based on location and morphology, aided by scanning electron micrographs of injected gerbil cochlear microvasculature,

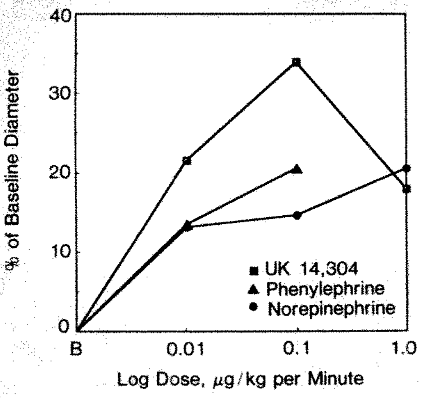

Fig 6.—The magnitude of constriction of the arterioles in response to UK 14 304, phenylephrine, and norepinephrine. This is expressed in percent of change in diameter from baseline vs the log of the drug concentration infused.

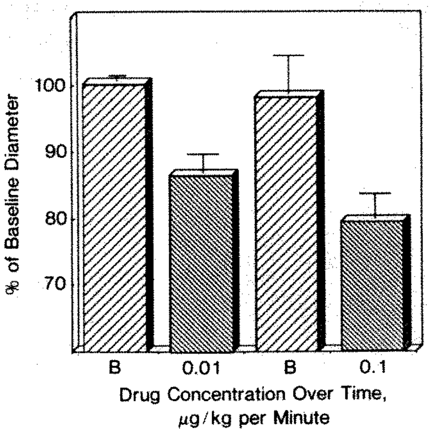

Fig 7.—Response to phenylephrine. Intrinsic radiating arteriole vascular tone (bars labeled "B"), set at 100%, is achieved between doses with maximal responses of 22% at 1.0 μg/kg per minute. The other two bars represent the dose of phenylephrine infused and the percent of decrease from baseline arteriole diameter. The time span is 120 minutes, with the baseline period being 10 minutes long and the subsequent intervals each being 20 minutes.

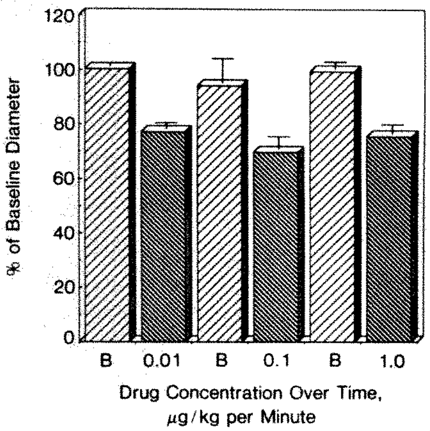

Fig 8.—UK 14 304 caused a substantially greater decrease in diameter at each dose, returning to baseline (bars labeled "B") between doses. The other three bars represent the dose of UK 14 304 infused and the percent of decrease from baseline arteriole diameter. The time span is 120 minutes, with the baseline period being 10 minutes long and the subsequent intervals each being 20 minutes.

as well as by the direction and velocity of blood flow. Diameter measurements were obtained from the identical position and tracked on a minute-to-minute basis. Measurements were made using a computer-generated "rubberband" line that displayed the starting and end point x and y coordinates as well as the color index values. This permitted detection in the processed image of the vessel edge, which was set at a recognizable value. The measurement cursor ("rubberband" line) was displaced on pixel inward on either side from the vessel edge point to obtain an intraluminal diameter measurement. The measurement system was calibrated against a digitized image of an etched optical caliper.

RESULTS

A total of 31 arterioles derived from 10 animal experiments was studied. These experiments included 3 in the norepinephrine group, 3 in the phenylephrine group, and 4 in the UK 14 304 group. At least 3 arterioles were examined in each experiment for a total of 9 diameter measurements per minute per drug. Vessel diameter data from a representative norepinephrine experiment are shown in Fig 4, which demonstrates that a steady state is achieved for several minutes during baseline periods as well as during application of intravascular ligand. This curve verifies that an adequate time period for ligand-receptor interaction and engagement of vascular smooth-muscle contractile mechanisms (with maximal effect) had elapsed.

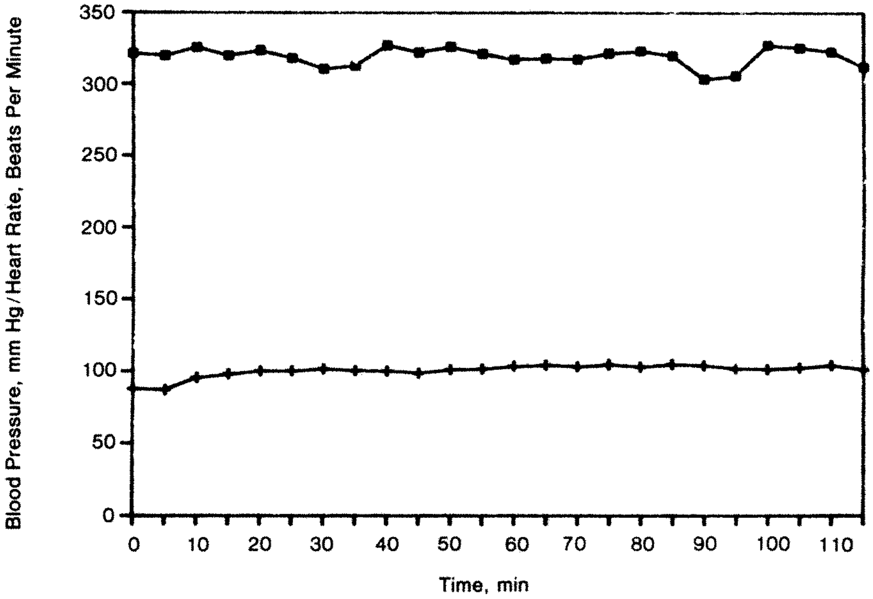

Fig 9.—Average heart rate (upper line) and blood pressure (lower line) responses to norepinephrine at 5-minute intervals are displayed to show no change during the experiment.

The baseline data accumulated in the beginning of each experiment permitted each animal to serve as its own control. This provided initial arteriole diameters, heart rate, and blood pressure measurements for subsequent comparison. The initial arteriole diameters were averaged into 5-minute intervals and set at 100%. This permitted subsequent arteriole diameter changes to be expressed as percent of change compared with baseline diameter (100%) and conversion to dose-response relationships.

The group response to norepinephrine application is shown in Figs 5 and 6. In Fig 5, the radiating arteriole diameters are returning to 100% of control diameters between doses. At

0.01 μg/kg per minute, the diameters (mean ± SD) are 86.8% ± 1.6% of control; at 0.1 μg/kg per minute, 85.4% ± 2.0% of control; and at 1.0 μg/kg per minute, 79.5% ± 3.3% of control. Figure 6 compares the dose-response relationships of all three drugs. Norepinephrine achieves a maximum 20.5% ± 3.3% decrease in vessel diameter at 1.0 μg/kg per minute.

Phenylephrine administration achieved 86.5% ± 2.7% constriction at 0.01 μg/kg per minute and 79.5% ± 3.4% constriction at 0.1 μg/kg per minute, with return to 100% baseline diameter between dose infusions (Fig 7). The dose-response relationship showed a maximal response at 0.1 μg/kg per minute of 20.5% ± 3.7%.

The UK 14 304 experiments (Fig 8) show substantial constriction: 77.4% ± 2.0% of control at 0.01 μg/kg per minute, 69.74% ± 4.9% of control at 0.1 μg/kg per minute, and 75.57% ± 3.5% of control at 1.0 μg/kg per minute. The UK 14 304 dose-response relationship (Fig 6) is interesting in that there is an upward trend between baseline and the 0.1 μg/kg per minute concentration portion of the curve. Arteriole diameter displays consistent decrease per minute until that point on the curve. The 0.1 to 1.0 μg/kg per minute portion of the curve has a decrease in slope associated with the tenfold *increase* in ligand concentration per minute. It should be noted that the percent of change in arteriole diameter from baseline at the 0.01 concentration compared with the same concentration of norepinephrine was significantly different ($P < .05$). Establishing significance at the two higher dosages (0.1 and 1.0 μg/kg per minute) of UK 14 304 compared with norepinephrine revealed substantial differences ($P < .001$) in percent of change of arteriole diameter from baseline at both concentrations.

The heart rate and blood pressure data demonstrate no change from baseline with administration of drugs. Figure 9 depicts a representative norepinephrine experiment. The AICA was monitored for change in diameter compared with baseline at the end of each drug infusion period and was found to be within 4% of control diameters.

The video photomicrographs (Figs 10 through 12) outline the computer-assisted video image processing of the intravital microscopic information. The AICA in the form of a fluorescent microangiogram is displayed, as are radiating and precapillary arterioles viewed through a window (approximately 700 × 800 μm) on the second turn of the cochlea. Figure 12 shows how an image appears after processing. The vessel edge was color index-shifted to zero (black) for computer recognition.

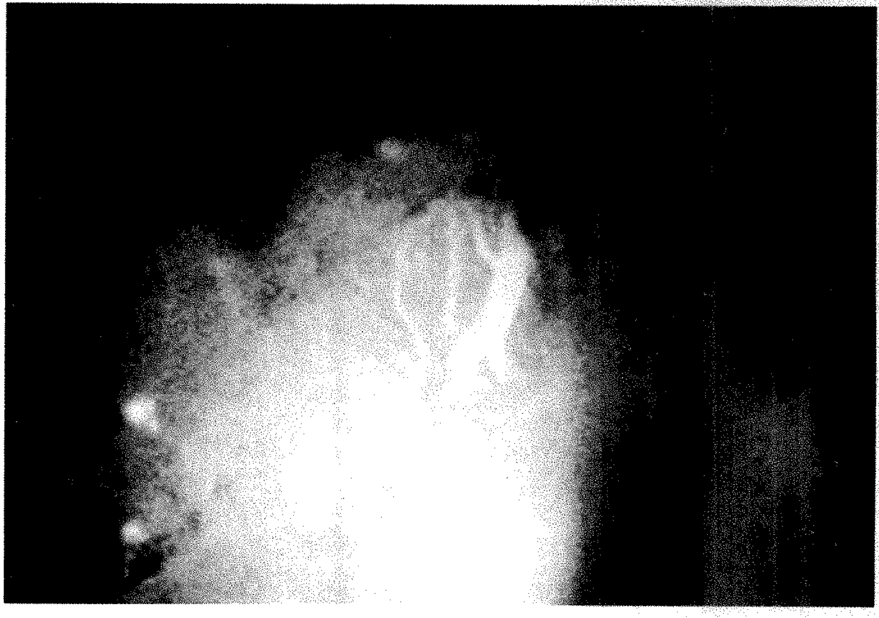

Fig 10.—Fluorescent video-photomicrograph of anterior inferior cerebellar artery (×60).

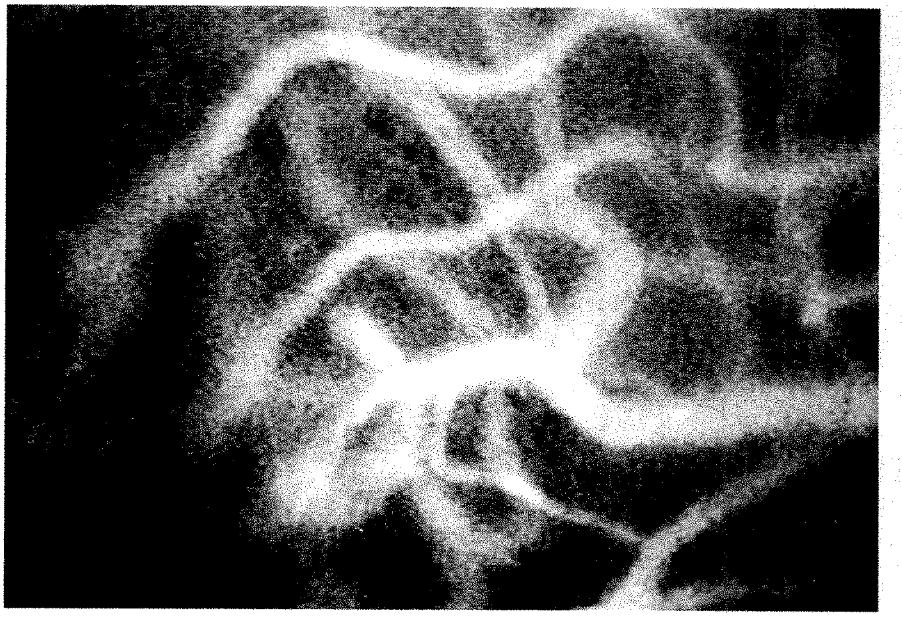

Fig 11.—Unprocessed fluorescent video-photomicrograph of radiating and precapillary terminal arterioles viewed through a window in the second turn of the cochlea (×675).

COMMENT

Despite substantial advances in the field of conductive hearing loss, the causes of presbycusis, Meniere's dis-

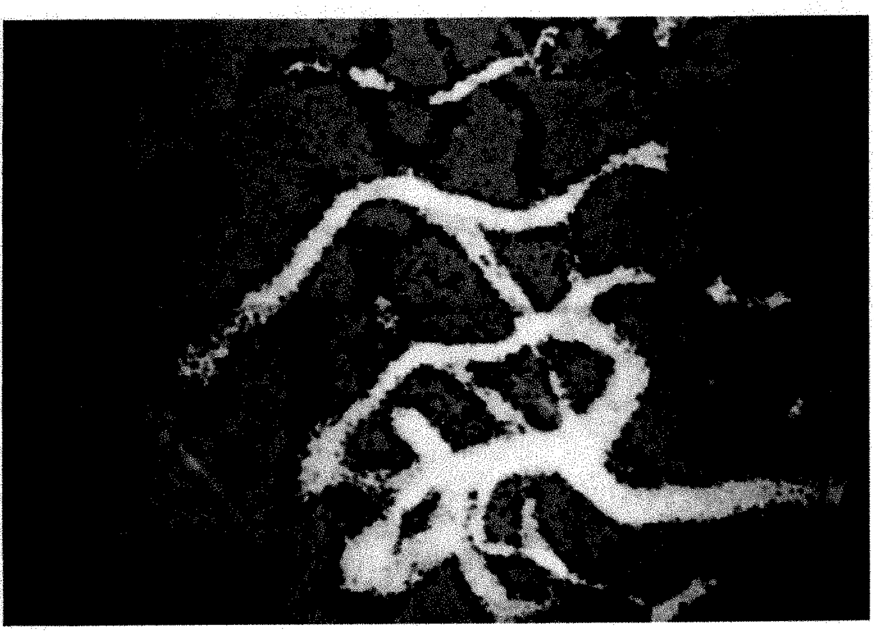

Fig 12.—The vessels in Fig 11 were digitally image-processed for vessel edge determination (×675).

ease, and sudden and fluctuant sensorineural hearing loss are still unknown. A variety of vasoactive drugs and osmotic agents have been used to treat these conditions, based on their known action in other vascular beds, often with unexpected or anomalous results. There is no direct evidence to explain their action on cochlear microcirculation. Moreover, the regulatory features of cochlear microcirculation remain largely unknown.

The microvasculature is believed to be controlled by several systems: metabolic, autoregulatory, myogenic, neural, and humoral.[14] Recently, it has become evident that the distribution of adrenergic nerves differs in various microcirculatory beds.[14] In most tissues, excluding the brain and myocardium, sympathetic vasoconstrictor nerves exert considerable tonic activity, and vasodilation occurs when sympathetic nerve stimulation is reduced. Adrenergic fibers originating in the ipsilateral superior cervical ganglion innervate both pial and intracerebral vessels. The effects of cerebral adrenergic nerves are substantially less pronounced (and by many authors considered negligible) than those seen in other vascular beds.[15,16] At the level of the cochlea, histochemical methods have demonstrated the presence of catecholaminergic nerves on terminal and radiating arterioles before they branch into the stria vascularis.[4] Hultcrantz and Angelborg[17] have reported that electrical stimulation of the cervical sympathetic chain decreases cochlear blood flow by 25%. The mechanism of this response is not clear. It is not known whether this is due to the presence of adrenergic receptors mediating constriction, ie, α adrenoreceptors, a passive response from shunting of blood to other cranial regions, or a myogenic response resulting from an elevation in arterial pressure during stimulation.

Establishing the presence and distribution of adrenergic receptors in cochlear microcirculation is needed to define basic mechanisms of control and to permit pharmacologic manipulation of blood flow in the inner ear. The present investigation measured arteriolar responses to the administration of α-adrenergic agonists by close intra-arterial infusion. This approach was selected because it minimized systemic drug administration, preventing alterations in heart rate and systemic arterial pressure that could produce myogenic and metabolic alterations at the level of the cochlear microvasculature. The retrograde cannulated carotid artery and extremely low infusion rate assured that the infusate, when it reached the brachiocephalic trunk, streamed into the subclavian artery, right vertebral artery, and on into the common cochlear artery and did not enter the aorta. This provided regionalized high drug concentration in the cochlear vascular bed while diminishing systemic effects from drug recirculation. Direct arterial puncture was considered because of the accessibility of the common cochlear artery. This would provide direct cochlear infusion of drug, but we felt that direct puncture of a terminal artery of this magnitude (60 to 70 μm) would significantly perturb the cochlear microcirculation.

Drug concentrations were carefully chosen to prevent both systemic responses and any effect of the drugs on the upstream AICA. These requirements put extreme limitations on the doses of drugs that could be used and prevented generation of complete dose-response curves. The lack of demonstrable AICA vasoactivity responses to these agents, at the administered concentrations, minimized any upstream contribution by this vessel to observed downstream effects in the cochlear microvasculature. This finding is consistent with the reported relative insensitivity of cerebral arteries to norepinephrine at physiologic pH.[16] However, we did not observe an α receptor-mediated cerebral arterial dilation in response to norepinephrine in either the arterioles or the upstream AICA.[18]

The lack of significant baseline alteration of heart rate and blood pressure throughout the experiments indicates that the observed radiating arteriole diameter changes were not secondary to active or passive responses due to mean or pulse pressure changes. On the contrary, our results demonstrate direct arteriolar vasoconstriction in response to the intraluminal α-adrenergic agonists and demonstrate the existence of both α_1 and α_2 adrenoceptors in this microvascular bed. The maximal arteriole constriction achieved by norepinephrine was approximated by phenylephrine and superceded by UK 14 304. This is quite significant when the relative potency and selectivity of these drugs are taken into consideration. Norepinephrine is typically selected for its ability to attain maximal α-adrenergic vascular smooth-muscle contraction and serves as the standard for comparison of effects of other adrenergic agonists. It can achieve effects in concentrations 10 to 100 times less than UK 14 304.[13] Phenylephrine is a highly selective α_1 receptor agonist, second only to methoxamine in selectivity, and exceeding norepinephrine by greater than 50 times.[6]

The phenylephrine response demonstrates the presence and ability of α_1 receptors to modulate cochlear blood flow. The ability of UK 14 304 to cause a substantial decrease in arteriolar diameter compared with norepinephrine suggests that a dense population of α_2 adrenoreceptors exists on the radiating arteriole as well. This is suggested by comparing the strong response and relative potency of UK 14 304 with those of norepinephrine and phenylephrine. The steep slope of the first portion of the dose-response curve indicates a high sensitivity to α_2 stimulation at the radiating arteriolar level. The curve at the higher dose (1.0 μg/kg per minute) showed a lower slope than expected, demonstrating a falling off of the percent of change in diameter per minute. This may indicate that the higher ligand concentration (1.0 μg/kg per minute) initiates upstream constriction of an arteriole that has a lower population of α_2 receptors, and, therefore, requires the higher concentration of drug to constrict. This would alter the downstream resting length-tension relationship of the vascular smooth muscle by decreasing pressure and generating a competing dilatory effect. The observation that the AICA maintained its baseline diameter at this point isolated the unmonitored portion of this system as the modiolar artery. Constriction of this vessel would explain the upstream effect. These findings are in agreement with observations in rat cremaster muscle preparations in which terminal arteriole constriction is mediated predominantly by α_2 adrenoreceptors and large (first order) arteriole constriction is mediated by both α_1 and α_2 receptors.[11]

In conclusion, radiating arterioles were observed to constrict in response to regional intravascular application of α-adrenergic agonists. This indicates that the peripheral cochlear arterioles are subserved by both α_1 and α_2 adrenoreceptors. Our findings indicate that these arterioles have a predominance of α_2 receptors. They also suggest that regulation of the cochlear microvasculature is independent of brain and is probably at the level of the radiating arteriole. It has its own receptor configuration and, unlike brain, it responds to norepinephrine at physiologic pH.

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An Estimate of the Prevalence of Tinnitus Caused by Spontaneous Otoacoustic Emissions

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• Prototypical experimental tests for linking spontaneous otoacoustic emissions with disruptive tinnitus have been described previously. Using similar experimental tests on 96 tinnitus sufferers, an estimate is made here of the prevalence of tinnitus caused by spontaneous otoacoustic emissions: the 95% confidence limits of this estimate are 1.11% and 9.05%.

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In an important article on tinnitus, Wegel[1] noted that a test tone sounded "pure and smooth" except when its frequency interacted with his tinnitus, in which case the two sounds beat with each other. This report has been widely cited and has led to many attempts to produce beats between tinnitus and external tones. Such efforts were not generally fruitful. Indeed, even Fowler,[2] a well-motivated experimenter afflicted with tinnitus, was unsuccessful in his attempts. The general failure to produce beats suggests that tinnitus that beats with external tones may be quite rare. Objective tonal tinnitus that can be heard on auscultation is one form of tinnitus in which external tones do beat with the tinnitus, but it is also probably uncommon,[3-8] and patients with it are often unaware of their tinnitus. (For the purposes of this article, tinnitus is defined as the conscious experience of sound that is annoying and irritating and originates in the head. Thus, if a spontaneous otoacoustic emission [SOAE] is annoying, it is referred to in this article as tinnitus.)

Spontaneous otoacoustic emissions (acoustic energies that can be detected when a sensitive miniature microphone is inserted into the meatus) do beat with external tones, and are far more common than are audible high-frequency tonal acoustic emissions. Various estimates of the prevalence of SOAEs indicate that 28% of men and 56% of women have SOAEs (R.C. Bilger, PhD, personal communication, 1988), although an even greater prevalence may arise as microphones become increasingly sensitive.[9]

In a previous report,[10] I presented evidence that SOAEs can be the source of disruptive tinnitus. The purpose of this report is to provide an estimate of the prevalence of SOAE-caused tinnitus. This issue is important for both scientific and clinical reasons. Scientifically, SOAEs could be the likely source of tinnitus when beats appear. Clinically, because aspirin abolishes SOAEs,[11] a palliative for some cases of SOAE-caused tinnitus may be readily available. Because there are few reported instances in which beats with tinnitus occur, SOAEs probably are not a frequent source of tinnitus. Nonetheless, the prevalence of SOAE-caused tinnitus is of interest.

Most investigators have linked SOAEs with tinnitus whenever the frequency of the SOAE was "near" the average frequency of a pure tone said to match the tinnitus pitch.[12-16] A summary of the existing data based on this criterion is presented in Table 1. For each study, only patients reporting the presence of tinnitus were included and the patients were not preselected for having any particular pathologic condition or audiometric configuration. Table 1 shows that of 205 patients, 9 (4.4%) were judged to have SOAE-caused tinnitus. The 95% confidence limits for this estimate are 2.02% and 7.61%. These limits employed an angular transformation of the binomial

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Table 1.—Summary of Existing Reports of Tinnitus Caused by Spontaneous Otoacoustic Emissions (SOAEs)

Source, y	Total No. of Patients	No. of Patients With SOAE-Caused Tinnitus
Wilson and Sutton,[12] 1981	11	4
Zurek,[13] 1981	6	0
Tyler and Conrad-Armes,[14] 1982	25	0
Wilson, 1983*	50	2
Hazell,[15] 1984	53	2
Rebillard et al,[16] 1987	60	1
Total	**205**	**9**

*Cited in Hazell,[15] 1984

variate ($p = 4.4\%$), which represents the prevalence estimate. The angular transformation of the binomial variate is used to set the confidence interval and the resulting interval is transformed back to proportions.

The transformation is employed because it produces a normally distributed variate whose variance is independent of p, whereas the variance of the binomial distribution depends on p.[17,18] The angular transformation produces a confidence interval in which arcsine p is the arithmetic center but p itself is not. In percentage terms, the confidence limits indicate that the prevalence of SOAE-caused tinnitus is low but not zero. In terms of the numbers of people potentially afflicted, these small percentages probably translate into large numbers. For example, if 17% of the American population has tinnitus, as was estimated recently for the British population,[19] then between 0.8 and 3.10 million people may have disruptive tinnitus caused by SOAEs.

There is, unfortunately, some difficulty in using existing publications to estimate the prevalence of tinnitus because the estimates are based on correlational data: the fact that the frequency of the SOAE and the frequency of a pure tone said to match the tinnitus pitch coincide does not prove that the SOAE causes the tinnitus. To link SOAEs with tinnitus, the tinnitus must disappear when the SOAEs are suppressed.[20] Additional circumstantial evidence is provided if the frequency of a tone matching the pitch of the tinnitus is near the SOAE frequency and if the isomasking contour for the tinnitus is not flat. Penner and Burns[20] stressed that the first test is preferable to the second and third because the latter two present merely circumstantial, correlational evidence, whereas the first is causal. The results of all three tests are used here to estimate the prevalence of SOAE-caused tinnitus.

PATIENTS AND METHODS

Patients

All listed members of the 121-person Washington (DC) area Tinnitus Self-Help Group were asked to participate, and 50 complied. Forty-six additional participants responded to signs posted at the University of Maryland, College Park, to recruit tinnitus sufferers and were included in this study. Thus, there was a total of 96 participants. The selection criterion was the reported presence of severe, troublesome tinnitus, and in no way involved suspected etiology of the tinnitus or audiometric configuration. Based on the data gathered in the first 2-hour session, patients suspected of having SOAE-caused tinnitus were asked to return for additional testing. Written consent to participate in the experiment was given by each patient after the nature of the procedures had been explained.

Apparatus

The apparatus was identical to that described previously.[10,20] A brief summary follows.

Pitch Matches and Isomasking Contours.—The timing and presentation of the stimuli were controlled by a laboratory computer. All tones were generated by a sine-wave oscillator and were gated exponentially (10-millisecond rise-fall time) at the positive-going zero crossing. Patients were tested individually and were seated in a double-walled chamber (Industrial Acoustics Co).

SOAE Measures.—The SOAEs were measured using standard techniques. A sensitive probe microphone (model ER-10, Etymotic Research, Elk Grove Village, Ill) was placed in the ear canal by the patient, who was seated in a sound attenuating chamber. The construction of the probe included two 1.35-mm (diameter) earphone coupling tubes mounted to pass through the 3.8-mm (diameter) probe tubing, permitting the delivery of stimuli from two independent (Etymotic ER-2) insert phones. The signal from the microphone was amplified and served as input to a Wavetek spectrum analyzer (model 5810A, Wavetek Corp, San Diego, Calif). Real-time spectra (0.00125-kHz line-spacing) were averaged (512 times) to improve the signal-to-noise ratio. The SOAEs appeared as spikes above the noise floor. If an SOAE seemed to be present, a second scan was initiated. If a spike appeared on two consecutive scans, it was considered a possible emission. Precise measurement of the frequency and amplitude was then made with a movable cursor. If similar spikes occurred in a second session during which the SOAE was to be suppressed, the spike was labeled as an emission.

Procedure

The procedures for suppressing the SOAEs, matching the tinnitus pitch, and measuring isomasking contours for tinnitus are also identical to those described previously.[10,20] A brief description of these procedures follows.

Matching the Tinnitus.—To estimate the predominant pitch of the tinnitus for the university subjects, the method of limits was employed.[21] Briefly, the frequency of a pulsed tone (1 second on, 1 second off) was changed continuously until the patient reported that a match had occurred. Each patient made 10 matches. As in the 1983 approach, a check for the possible occurrence of octave confusion followed each match. No apparent octave confusions were observed.

Isomasking Contours.—The maskers had a duration of 1 second and were presented at 30 per minute. The patient controlled the intensity of the masker with a response panel and was instructed to adjust the intensity of the masker until the tinnitus was not audible. A masking run was terminated by a button push from the patient or when the level reached 90 dB sound pressure level. Details of the procedures involved in obtaining masking patterns were described by Penner and Burns.[20]

Suppression of SOAEs.—For patients with a single SOAE, an external tone with a frequency near the SOAE frequency was presented at a low volume and then increased in volume until the SOAE was suppressed into the noise floor. For patients with two or more SOAEs over a relatively narrow range (on the order of 1.5 kHz), a suppressor with a frequency of approximately the mean frequency of the extreme SOAEs were adjusted in volume until all of the SOAEs were suppressed. In all cases, when the emission(s) had been suppressed, the patients were asked (1) whether they were aware of the external tone, and (2) whether their tinnitus was still present and, if so, if it had been affected in any way.

Tinnitus Masking Demonstration.—The maskers were presented at a level approximately 10 dB above the masked threshold, using the insert earphone attached to the microphone probe assembly. The patient was asked if the tinnitus was indeed masked, and the SOAE was measured to see if it was still present.

RESULTS

The data for each patient are presented in Table 2. The first 4 patients listed in the table were judged to have SOAE-caused tinnitus because the tinnitus was not audible when the SOAE was suppressed. The next 48 patients were from the self-help group, and the next 44 from the university group. Within each group, the patients were studied in the order presented in Table 2 except that the first 4 patients were actually patients 16 and 50 (in the self-help group) and 92 and 93 (in the university group). These 4 patients' data are listed first to facilitate finding the data belonging to the patients with SOAE-caused tinnitus. The university patients were all tested before the self-help group patients. To assist in assimilating these data, some summary statistics describing the patients are described below, followed by a discussion of the SOAE-tinnitus link for the first 4 patients.

Tinnitus and Gender

Significantly more men (69) than women (27) were tested ($\chi^2 = 18.4$; $df = 1$; $P < .01$). This is somewhat surprising because a British survey[19] reported that, even though more men than women in their sample had sensorineural hearing loss, there were roughly equal percentages of men and women suffering tinnitus in Britain. If a similar equality held in the United States and if the present patients represented a haphazard sample of sufferers, then an equal number of male and female patients might be expected in this study. The preponderance of men was not due to the selection procedure itself: of the 166 potential participants (121 from the self-help group and 45 from the university), 102 were men.

Table 2.—Results of the Search for SOAEs in 96 Tinnitus Sufferers*

	Tinnitus			SOAE‡		
Patient No./Sex/Location of Tinnitus†	Suspected Cause	Duration, y	Frequency, kHz	Frequency, kHz	Intensity, dB SPL	PTA, dB SPL
50/M/B	Noise	6	1.411; 1.302	1.344; 1.201	−2.7; 1.3	−1
16/F/R	Noise	8	1.525; 1.751	1.416; 1.887; 1.100	10.1; 9.3; 2.0	11
93/F/R	Ear infection	1	1.085	1.525; 1.950	1.4; 0.0	1
92/F/R	Noise	10	1.217	1.268	8.7	6
1/F/B	Noise	30	...	...	...	...
2/F/L	Meniere's disease	...	3.010	...	...	...
3/M/R	...	2	7.477	...	...	...
4/M/B	Head injury	30	7.840	...	...	...
5/M/B	...	2	14.528	...	...	...
6/M/H	Noise	5	6.281	...	...	...
7/M/B	Noise	4	2.825	...	...	...
8/M/B	...	7	5.242	...	...	...
9/M/B	...	10	3.321	...	...	...
10/F/R	...	5	1.948	...	...	...
11/M/H	...	12	4.719	...	...	...
12/F/B	...	8	3.919	...	...	23
13/M/B	Head injury	41	3.766	...	...	...
14/M/B	Noise	7	2.720	...	...	...
15/M/B	...	30	5.938	...	...	...
17/M/B	...	10	1.549	...	...	...
18/M/B	...	17	5.702	...	...	...
19/F/H	...	5	...	...	...	...
20/M/B	...	10	2.836	...	...	...
21/F/B	Noise	4	1.856	...	...	...
22/M/L	...	20	3.234	...	...	...
23/F/R	...	25	2.379	...	...	31
24/F/R	Noise	1	4.829	...	...	...
25/M/B	Age, noise	20	3.193	...	...	19
26/M/B	...	42	3.601	...	...	9
27/M/R	Meniere's disease	12	4.414	...	...	−13
28/F/B	Meniere's disease, noise	6	4.073	1.000; 1.125	−0.4; −1.2	...
29/M/B	...	4	0.258	...	...	18
30/F/B	Noise	1	0.781	...	...	39
31/M/B	Noise	42	3.333	...	...	24
32/F/B	Noise	25	0.164	...	...	38
33/M/B	Noise	20	6.534	...	...	...
34/M/R	Heredity	36	3.581	...	...	23
35/M/B	Noise	2	...	...	...	−6
36/M/H	Medication	5	4.331	...	...	4
37/M/B	...	3	4.793	...	...	6
38/M/B	...	2	3.660	...	...	−6
39/F/R	Noise	0.12	...	...	...	8
40/M/B	...	2	3.283	...	...	14
41/M/B	Medication	3	3.064	...	...	41
42/F/B	...	22	...	...	...	...
43/M/R	...	18	7.430	...	...	13
44/F/U	...	12	0.632	...	...	28
45/M/B	Meniere's disease	60	2.810	...	...	20
46/F/H	...	...	3.609	...	...	23
47/M/H	...	5	5.365	...	...	14

*Searches for spontaneous otoacoustic emissions (SOAEs) were made from 0.025 to 20 kHz. For the self-help group, the patient number represents the actual sequential order in which the patient was tested. For the university group, the number obtained when 50 is subtracted from the patient number represents the serial position of that patient within the group.

†B indicates binaural; R, right; L, left; H, head; and U, unsure.

‡Frequency values are average frequencies of 10 matches to the tinnitus pitch. SPL indicates sound pressure level.

Table 2.—Results of the Search for SOAEs in 96 Tinnitus Sufferers* (cont)

	Tinnitus			SOAE‡		
Patient No./Sex/ Location of Tinnitus†	Suspected Cause	Duration, y	Frequency, kHz	Frequency, kHz	Intensity, dB SPL	PTA, dB SPL
48/M/B	...	5.5	3.684	...	...	8
49/F/H	...	2	...	...	...	6
51/M/R	Viral	2	0.871	...	...	3
52/M/L	Kanamycin	27	2.552	...	...	40
53/M/R	Illness	11	2.880	...	...	11
54/M/B	Otosclerosis, surgery	6	2.136	...	...	44
55/M/B	Noise	20	2.353	...	...	18
56/M/U	Noise	5	...	...	...	−6
57/M/U	Noise	Unsure	8.075	...	...	11
58/M/B	Head injury, noise	15	8.229	...	...	39
59/M/B	Noise	43	2.515	...	...	...
60/F/B	Noise	5	3.263	1.118; 1.294	0.3; 8.4	−1
61/M/B	Noise	7	...	...	...	32
62/F/B	Allergy ear infection	Unsure	4.683	...	...	8
63/M/U	Noise	3	6.017	...	...	−7
64/F/U	...	Unsure	1.338	...	...	26
65/M/U	...	Unsure	4.445	...	...	23
66/F/B	...	Unsure	6.279	...	...	19
67/M/B	Stress	5	3.373	...	...	14
68/M/B	Sudden hearing loss	3	3.530	5.275	1.3	−6
69/M/L	Noise	28	6.150	...	...	6
70/M/B	Noise	21	3.011	...	...	...
71/M/R	...	50	1.250	...	...	11
72/M/B	Noise	6	5.102	...	...	1
73/M/R	Ear infection	7	6.130	2.250	−1.6	4
74/M/L	Noise	33	3.978	...	...	14
75/M/R	Ear infection	6	3.405	...	...	9
76/M/L	Noise	10	4.444	...	...	8
77/M/R	Ear infection	29	6.066	...	...	17
78/M/B	Ear infection, noise	20	4.758	...	...	6
79/M/R	Noise	2	5.083	...	...	9
80/M/B	Head injury, illness	5	11.410	...	...	−1
81/M/L	Noise	3	3.500	...	...	3
82/M/L	Noise	13	9.015	1.750	1.4	8
83/M/B	Ear infection, noise	25	2.946	...	...	18
84/M/B	Unsure	8	3.030	...	...	3
85/F/U	Ear infection	6	3.265	...	...	28
86/M/R	Noise	3	8.691	...	...	9
87/F/R	Ear infection, noise	7	4.259	1.875	4.6	−8
88/M/B	Infection, head injury, noise	30	0.414	...	...	1
89/M/B	Noise	Unsure	3.175	...	...	12
90/M/R	Unsure	2	6.234	...	...	−7
91/F/B	Unsure	7	4.599	...	...	11
94/F/B	Surgery	13	5.685	...	...	30
95/M/L	Noise	2	0.513 3.949	...	...	9
96/M/L	Viral	2	0.871	...	...	10

Lateralization of Tinnitus

Fifty-one patients reported that their tinnitus was binaural, 10 that it was monaural in the left ear, 21 that it was monaural in the right ear, and 7 that it was "in the head"; 7 were not sure of the location. Given that small differences in intensity can move the apparent image in the head toward the ear receiving the more intense sound, it is entirely possible that reports of monaural tinnitus are not valid. Ignoring this important qualification and that of accepting self-report as a measure, approximately 32% of the patients had monaural tinnitus. This estimate is similar to Vernon's finding[22] that 37% of all tinnitus is reported to be monaural.

Suspected Cause of Tinnitus

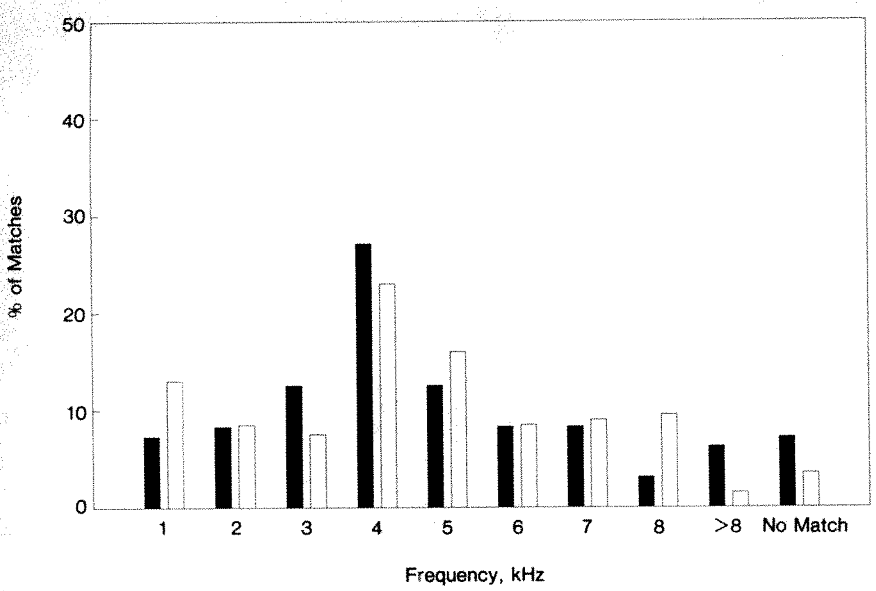
Noise exposure was the factor most frequently reported as the suspected cause of tinnitus (40 cases), with ear infection (or viral infection) a distant second (12 cases). Thirty-one of the patients did not report a suspected cause. Other factors listed included head injury, otosclerosis, allergy, medication, stress, and surgery.

Pitch of the Tinnitus

The average frequency of repeated matches of an external tone to the predominant pitch of the tinnitus by a single patient is reported to be quite variable.[21,23,24] The data collected here and presented in the Figure also display considerable variability for a single match across patients. For comparison, Reed's data,[25] based on 200 patients, are also displayed. Note that there is good agreement between the two sets of results in that both display a concentration of matches to the tinnitus in the 3- to 5-kHz region. It is important to realize that pitch matching does not indicate that the tinnitus "sounds like" the pure tone to which it is matched.

SOAEs

SOAEs were detected in 3 members (2 women and 1 man) of the self-help group and in 7 members (4 women and 3 men) of the university group. Thus 10 (10.4%) of 96 of those with tinnitus also had SOAEs. Of the 40 people with noise damage, 3 (7.5%) had emissions. This percentage compares favorably



Frequency distribution of matches to tinnitus. Bin widths are 1 kHz except for the two bins on the extreme right. The numbers on the abscissa represent the upper limit of the matches. Solid bars represent data from the present study; open bars, data from Reed.[25]

with the 7% reported by Probst et al.[26] Note also that we would expect to find significantly fewer men than women with SOAEs if the prevalences of SOAEs in the normal-hearing population and among tinnitus sufferers were the same.

Tinnitus and SOAEs

For 4 of the patients tested (2 from each group), SOAEs appeared to be the source of the tinnitus based on the tests discussed in the introduction. Briefly, for each of the first 4 patients listed in Table 2, the tinnitus was absent when the SOAE was suppressed, the frequency of a pure tone said to match the pitch of the tinnitus was near the SOAE frequency, and the isomasking contour using the tinnitus as the signal was not flat. Although the latter two tests provide only circumstantial evidence, the first test does implicate SOAEs as the source of tinnitus. Detailed data for 2 of these patients (patients 92 and 93) can be found elsewhere.[10,27]

The data in Table 2 show that each of these 4 patients had PTAs of 11 dB or less and the frequency of the tone matching the tinnitus pitch was in the 1- to 2-kHz region.

COMMENT

As shown in Table 2, 4.2% of the people had SOAE-caused tinnitus. The data in Table 1 show that despite the fact that the evidence used to link SOAEs and tinnitus is weak, the prevalence estimate for SOAE-caused tinnitus is within two tenths of 1% of the present 4.2% estimate. The numerical similarity of prevalence estimates may be fortuitous because the criterion in Table 1 for linking SOAEs with tinnitus has been demonstrated, at least for one patient, to fail.[28]

One important question emerging from this prevalence study involves identification of the characteristics of patients who are likely to have SOAE-caused tinnitus. At present, the scarcity of such patients probably precludes generalizations. Although reliable statements narrowing the field of candidates cannot yet be made, I hope that this report will motivate large-scale searches in clinics so that the psychophysical characteristics of patients with SOAE-caused tinnitus can eventually be enumerated.

The present data provide several hints as to the patient characteristics that future studies might explore. Note that for all four patients with SOAE-caused tinnitus, the frequency of the tone matching the pitch of the tinnitus is lower (1 to 2 kHz) than that typically matched to tinnitus unassociated with SOAEs (3 to 5 kHz) (Table 2). Furthermore, none of these patients had a large hearing loss at the SOAE frequency. Kemp[29] has argued that it would be worthwhile to continue to make acoustic measurements for a relation between SOAEs and tinnitus while selecting as patients those tinnitus sufferers with fairly normal hearing. The results in this and a previous article[10] have demonstrated audible SOAEs in just such patients.

Echoing Kemp's observation, the British survey[19] also found that approximately half of the people with severe tinnitus did not report having a measurable hearing impairment. Although it is certainly the case that high-frequency hearing loss might not cause a noticeable hearing impairment, it is also possible that the failure to report an impairment means that no impairment exists. If so, approximately half of all cases of severe tinnitus would arise among normal-hearing persons who often have SOAEs. Spontaneous otoacoustic emissions are not generally present unless the threshold is less than 20 dB hearing level.[26] Thus, if only the impaired reported having tinnitus, then SOAEs could probably be discounted as a source of tinnitus. The British survey therefore motivates a search for an auditory mechanism that produces tinnitus and yet does not greatly affect thresholds. SOAEs, which are generally associated with nearly normal hearing, are obvious candidates.

The importance of estimating the prevalence of SOAE-caused tinnitus and specifying characteristics of patients with this affliction lies in observing that SOAE-caused tinnitus may be treatable. Aspirin can abolish SOAEs,[11] and if a dosage can be found that does not cause salicylate-induced tinnitus, then a palliative for disruptive tinnitus may be readily available. It is quite clear that some instances of tinnitus can best be explained by SOAEs,[1,10,27] but the prevalence estimate provided here is an important indication of the total number of such cases.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Brain White-Matter Changes in the Elderly Prone to Falling

Joseph C. Masdeu, MD; Leslie Wolfson, MD; George Lantos, MD; Jonathan N. Tobin, PhD; Ellen Grober, PhD; Robert Whipple, MS; Paula Amerman, RN, MSN (*Arch Neurol.* 1989;46:1292-1296)

Impaired Recognition of Meaningful Sounds in Alzheimer's Disease

Steven Z. Rapcsak, MD; Mary Kentros, MD; Alan B. Rubens, MD (*Arch Neurol.* 1989;46:1298-1300)

Cortical Pathophysiology and Clinical Neurologic Abnormalities in Acute Cerebral Ischemia: A Serial Study With Single Photon Emission Computer Tomography

Mario Rango, MD; Olivia Candelise, MD; Daniela Perani, MD; Cristina Messa, MD; Guglielmo Scarlato, MD; Nicola Canal, MD; Massimo Franceschi, MD; Ferrucio Fazio, MD (*Arch Neurol.* 1989;46:1318-1322)

Correlates of Headache in a Population-Based Cohort of Elderly

Nancy R. Cook, ScD; Denis A. Evans, MD; H. Harris Funkenstein, MD; Paul S. Scherr, ScD; Adrian M. Ostfeld, MD; James O. Taylor, MD; Charles H. Hennekens, MD, DrPh (*Arch Neurol.* 1989;46:1338-1344)

The Development of the Dizziness Handicap Inventory

Gary P. Jacobson, PhD, Craig W. Newman, PhD

• Conventional vestibulometric techniques are inadequate for quantifying the impact of dizziness on everyday life. The 25-item Dizziness Handicap Inventory (DHI) was developed to evaluate the self-perceived handicapping effects imposed by vestibular system disease. The development of the preliminary (37 items) and final versions (25 items) of the DHI are described. The items were subgrouped into three content domains representing functional, emotional, and physical aspects of dizziness and unsteadiness. Cronbach's α coefficient was employed to measure reliability based on consistency of the preliminary version. The final version of the DHI was administered to 106 consecutive patients and demonstrated good internal consistency reliability. With the exception of the physical subscale, the mean values for DHI scale scores increased significantly with increases in the frequency of dizziness episodes. Test-retest reliability was high.

***(Arch Otolaryngol Head Neck Surg.* 1990;116:424-427)**

Quantifying the effects of medical, surgical, and rehabilitative management of the dizzy patient is problematic. Caloric testing is ineffective in evaluating treatment, since a unilateral weakness observed during the initial examination usually persists on reexamination. Although pretreatment and posttreatment rotary chair and platform posturographic testing may serve to document the process of central vestibular system compensation, these procedures are unable to quantify the effects of unsteadiness on everyday function. It appears, therefore, that conventional diagnostic tests are inadequate for evaluating the handicapping effects imposed by vestibular system disease.

Many clinicians either have developed their own or employ published dizziness questionnaires[1] in an attempt to qualitatively assess a patient's dizziness complaint. Although these instruments provide a systematic approach for obtaining case-history information, they are not useful in measuring the effects of therapeutic intervention. In response to the need for developing a method for quantifying the effects of treatment for Meniere's disease, the Committee on Hearing and Equilibrium of the American Academy of Ophthalmology and Otolaryngology[2] proposed a formula that determines the frequency of dizziness episodes before and after treatment. The formula consists of a ratio of the average number of dizziness spells a patient experiences per month 24 months after therapy, divided by the average number of spells per month 6 months prior to therapy. This quantity is multiplied by 100. Although this formula takes into account the frequency of dizziness attacks, it does not attempt to evaluate the impact of dizziness on the way a patient functions in everyday life.

We feel the method described above is shortsighted and limited in evaluating the treatment of vertigo. It is our contention that quantifying the handicapping consequences of dizziness may be a more useful means of validating treatment procedures. For example, patients who have experienced only a few attacks of violent vertigo may be sufficiently alarmed to the extent of restricting their activities (eg, quitting their occupations or avoiding social activities) so as not to be vulnerable should another attack of vertigo occur. It is reasonable to conclude that effective management of vestibular system disease should be reflected by an individual's ability to resume his or her premorbid vocational and avocational activities.

The present study was a natural evolution from work conducted by one of the investigators (C.W.N.) who recently employed the Hearing Handicap Inventory for the Elderly[3] before and after a hearing aid–fitting protocol to quantify benefits derived from amplification.[4] Similarly, we are suggesting that perceived dizziness handicap may be used as an index of treatment success over a selected time interval. That is, a well-designed scale could be employed to quantify changes in behavior that result from therapeutic intervention. The present scale was modeled after the Hearing Handicap Inventory for the Elderly and has been called the Dizziness Handicap Inventory (DHI).

The purposes of the present investigation were fourfold. First, we sought to develop a self-assessment inventory designed to evaluate the precipitating physical factors associated with dizziness as well as the functional and emotional consequences of vestibular system disease. Additionally, we undertook the present study to determine the internal consistency reliability of the DHI and to examine self-perceived dizziness handicap as a function of the frequency of dizziness or unsteadiness episodes. Finally, it was our intent to

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Table 1.—Internal Consistency Reliability Values (Chronbach's α) for the Preliminary and Final Versions of the Dizziness Handicap Inventory (DHI)

DHI Scale	Preliminary	Final
Total	.91	.89
Functional	.87	.85
Emotional	.72	.72
Physical	.74	.78

Table 2.—Final α Version of Dizziness Handicap Inventory With Corrected Item-Total Correlation Coefficients

Dizziness Handicap Inventory*

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing because of your dizziness or unsteadiness. Please answer "yes," "no," or "sometimes" to each question. *Answer each question as it pertains to your dizziness or unsteadiness problem only.*

Item	Item Total *r*
P1. Does looking up increase your problem?	.54
E2. Because of your problem, do you feel frustrated?	.34
F3. Because of your problem, do you restrict your travel for business or recreation?	.76†
P4. Does walking down the aisle of a supermarket increase your problem?	.39
F5. Because of your problem, do you have difficulty getting into or out of bed?	.50
F6. Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?	.69
F7. Because of your problem, do you have difficulty reading?	.44
P8. Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?	.54
E9. Because of your problem, are you afraid to leave your home without having someone accompany you?	.43
E10. Because of your problem, have you been embarrassed in front of others?	.46
P11. Do quick movements of your head increase your problem?	.51
F12. Because of your problem, do you avoid heights?	.49
P13. Does turning over in bed increase your problem?	.43
F14. Because of your problem, is it difficult for you to do strenuous housework or yardwork?	.58
E15. Because of your problem, are you afraid people may think you are intoxicated?	.30
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	.62
P17. Does walking down a sidewalk increase your problem?	.58†
E18. Because of your problem, is it difficult for you to concentrate?	.49†
F19. Because of your problem, is it difficult for you to walk around your house in the dark?	.48
E20. Because of your problem, are you afraid to stay home alone?	.27
E21. Because of your problem, do you feel handicapped?	.41
E22. Has your problem placed stress on your relationships with members of your family or friends?	.46
E23. Because of your problem, are you depressed?	.41
F24. Does your problem interfere with your job or household responsibilities?	.56
P25. Does bending over increase your problem?	.57

*A "yes" response is scored 4 points. A "sometimes" response is scored 2 points. A "no" response is scored 0 points.

†Questions with the highest corrected item-total correlation for each subscale. F indicates subscale. E, Emotional subscale; and P, Physical subscale.

assess test-retest reliability of the instrument.

INVESTIGATION 1

Methods

An initial pool of 37 items for the DHI was developed empirically from case-history reports of patients with dizziness. Items were tentatively grouped a priori into three content domains representing functional (16 items), emotional (10 items), and physical (11 items) aspects of dizziness and unsteadiness. The 37 items comprising the preliminary version of the DHI were selected to ensure that the scale had both content and face validity. An example of a probe question for functional aspects of dizziness would be: "Because of your problem, do you restrict your travel for business or recreation?" An example of a probe question for emotional aspects of dizziness would be: "Because of your problem, have you been embarrassed in front of others?" A probe question for physical aspects of dizziness would be: "Do quick movements of your head increase your problem?" The phrase *your problem* was used within each item instead of the descriptor *dizziness* so as not to influence the subject's response to each question by labeling the clinical complaint. For each item, the subject was instructed to respond by saying "yes," "no," or "sometimes."

The preliminary form of the scale was administered to 63 consecutive patients seen in our laboratory prior to their vestibulometric tests. There were 25 males and 38 females included in this group. The mean age of the subjects was 49.4 years (SD = 18.5), ranging from 21 to 82 years. The primary goal in evaluating the prototype inventory was to establish probe categories each with high internal consistency and a minimum number of items to make the DHI a more clinically efficient instrument. These data were tabulated and submitted to statistical analysis. The Cronbach α coefficient analysis was employed to measure reliability based on internal consistency. Corrected item-total correlations were performed to measure the strength of the relationship between an individual item and all remaining items in a subsection.[5] Because the α coefficient is a function of the item-total correlation, items with high item-total correlation values contribute more to a scale's reliability and may be considered more representative of the scale's content than the other items producing low item-total correlations.[6]

Results

Table 1 displays Chronbach's α values for the total and subscales for the preliminary version of the DHI. The α coefficients were high for the total scale (.91) and good for the subscales (.74 to .87).

The purpose of investigation 1 was to reduce the number of items on this scale based on the preliminary version of the inventory and maintain adequate internal consistency reliability. The corrected item-total values of the 37 items showed that a number of items could be deleted from the preliminary version based on low corrected item-total correlations. For example, the question: "Because of your problem, is it difficult for you to look at moving objects such as trains, merry-go-rounds, or buses?" that appeared in the functional subscale was omitted because it yielded a low corrected item-total correlation (.27), suggesting it was not consistent with the rest of the items in that section.

The item "Because of your problem, is it difficult for you to concentrate?" was placed initially in the functional subscale. This item demonstrated a weak corrected item-total correlation (.36) in the initial analysis. It was felt that this item might be better placed within the emotional subscale. When this item was transposed to the emotional subscale (the "Results" subsection of the "Investigation 2" section), the corrected item-total correlation improved to .49, suggesting that difficulty concentrating effects changes in the emotional realm.

A number of items from the preliminary version of the DHI were deleted because of their similarity in content. For example, the question: "Because of your problem, is it difficult for you to drive your car?" was eliminated in favor of: "Because of your problem, do you restrict your travel for

Table 3.—Means (SDs) for the Dizziness Handicap Inventory (DHI) by Frequency of Occurrence of Dizzy or Unsteady Episodes

Frequency of Occurrence	N	DHI Functional[*]	 Emotional[†]	 Physical[‡]	 Total[§]
Occasionally (≤12 times/year)	39	8.2 (7.5)	6.9 (6.5)	9.6 (6.2)	24.8 (17.8)
Frequently (>12 times/year but not continuously)	51	12.2 (9.8)	11.1 (8.9)	11.0 (7.1)	34.2 (21.9)
Continuously	16	18.5 (8.3)	16.4 (9.9)	14.4 (6.5)	49.1 (22.3)
Total	**106**	11.6 (9.2)	10.5 (8.8)	11.0 (6.8)	32.7 (21.9)

[*] Maximum score, 36.

[†] Maximum score, 36.

[‡] Maximum score, 28.

[§] Maximum score, 100. Sums in this column represent rounding.

business or recreation?" Both questions focused on traveling; however, patients could not answer the former question unless they were capable of driving, whereas passengers could answer the latter question.

The item "Because of your problem, do you think that people are less likely to be your friend?" that appeared in the emotional subscale was deleted following examination of this question's mean and SD scores. All but one subject had a "no" response, indicating that this item provided little or no information about individual differences between subjects.

These deletions resulted in a 25-item final version of the DHI having 9 functional, 9 emotional, and 7 physical questions. Scoring of the DHI is straightforward. A "yes" response to an item is awarded 4 points; "sometimes," 2 points; and a "no," 0 points. Thus, possible scores on the total scale range from 0, suggesting no handicap, to 100, indicating significant self-perceived handicap.

INVESTIGATION 2

Methods

The final version of the 25-item DHI underwent a randomization of questions and was administered to 106 consecutive patients (40 males and 66 females) seen for vestibulometric testing. The mean age of these subjects was 48 years (SD = 15.84), ranging from 15 to 85 years. This sample was divided into three subgroups based on the number of dizzy or unsteadiness episodes experienced by a patient over the past 12-month period. The subgroups were composed of those patients experiencing dizziness episodes occasionally (<12 times per year), frequently (≥12 times per year but not continuously), or continuously. There were 39 subjects in the "occasionally" subgroup, 51 subjects in the "frequently" subgroup, and 16 in the "continuously" subgroup.

Results

The results of this investigation were tabulated and analyzed using Chronbach's α coefficient. Table 1 shows the total and subscale α values for the final version. It may be observed that the deletion of the 12 individual items in investigation 1 (preliminary version) did not significantly affect the subscale or total coefficient α values of the final version. Table 2 shows the randomized final version of the DHI with the item-total corrected coefficient values. Questions with high values were considered the most representative items of their subscale. It was found that questions suggesting that dizziness or unsteadiness caused patients to "restrict travel for business or recreation" (functional subscale), have "difficulty concentrating" (emotional subscale), or have difficulty "walking down the sidewalk" (physical subscale) were the questions demonstrating the highest corrected item-total correlation. Their α coefficients were .76, .49, and .58, respectively.

Table 3 summarizes the means and SD of the DHI as a function of the frequency of occurrence of dizziness episodes. As shown in Table 3, mean values for total DHI scale scores increased with the number of dizziness episodes for the total subscales. A one-way between-subjects analysis of variance indicated a significant DHI total score main effect for frequency of occurrence (f = 8.17, $df = 105$, $P < .001$). Post hoc analysis yielded significant differences between all three groups (occasionally vs continuously, $t = 4.00$, $P < .001$; occasionally vs frequently, $t = 2.16$, $P = .03$; frequently vs continuously, $t = 2.54$, $P = .01$).

An additional series of 3 one-way analyses of variance were conducted to determine whether the frequency of dizziness episodes effected changes in self-perceived handicap for each of the subscales. With the exception of the physical subscale, the results of these analyses were identical to those obtained for the total DHI score. The main effects were significant for the functional (f = 8.06, $df = 105$, $P = .001$), and emotional (f = 7.89, $df = 105$, $P = .001$) subscales. The main effect for the physical subscale did not reach significance (f = 2.83, $df = 105$, $P = .06$). Accordingly, the relative frequency of dizziness or unsteadiness episodes did not appear to affect the level of self-perceived physical handicap in this group of patients. Alternately, the frequency of dizziness or unsteadiness episodes systematically affected the magnitude of self-perceived functional and emotional handicap.

Pearson product-moment correlations were conducted to determine whether subject age had an effect on the DHI total and subscale scores and, thus, on the magnitude of self-perceived dizziness handicap. Results demonstrated that the age of the patients imposed no systematic effect on self-perceived handicap as indicated by the total DHI score ($r = .01$, $df = 105$, $P = .89$), or the functional ($r < .01$, $df = 105$, $P = .94$), emotional ($r = < .01$, $df = 105$, $P = .94$) or physical subscales ($r = -.02$, $df = 105$, $P = .87$).

Finally, we were interested in determining whether there was any relationship between the results of a conventional test of vestibular system function and the total score on the DHI. A Pearson product-moment correlation was used to determine the level of association between the degree of caloric asymmetry (as measured on the alternate binaural bithermal caloric test) and the total score on the DHI. This analysis was conducted on 37 consecutive patients. The results failed to demonstrate a significant relationship between the two measures ($r = .09$, $df = 36$, $P = .58$).

INVESTIGATION 3

Methods

A group of 14 subjects (5 males and 9 females) ranging in age from 26 to 71 years (mean, 45 years) (SD = 13.48 years) were administered the scale at two separate occasions to determine test-retest reliability of the DHI. The scale was administered in a face-to-face format on the morning of vestibulometric testing, and then again at the end of the same day following testing and an ear, nose, and throat examination. The magnitude of random measurement error in test and retest scores can be assessed by administering the test within a relatively short time period.[7]

Results

Pearson product-moment correlations were computed for the total DHI scores between the first and second administrations of the DHI. The test-retest reliability for the total score was excellent ($r = .97$, $df = 12$, $P < .0001$). Similarly, correlation coefficients associated with the functional ($r = .94$), emotional ($r = .97$), and physical ($r = .92$) subscales were high and statistically significant ($P < .001$) as well.

The SE of measurement and the SE of the difference between two administrations of the DHI were calculated. Accordingly, SE = 6.23, suggesting that pretreatment and posttreatment scores would have to differ by at least 18 points (95% confidence interval for a true change) before the intervention could be said to have effected a significant change in a patient's self-perceived dizziness handicap.

COMMENT

There has been a renewed interest in recent years in developing self-assessment techniques designed to explore and quantify how patients react to their disability. These self-assessment scales have focused on patients with hearing loss[3,6-8] and tinnitus.[9] It is surprising that until now, with few exceptions,[10-12] there has been a lack of interest in the global effect that disequilibrium has on a patient's life. We felt it important to develop a self-assessment inventory to assist in clinical management decisions for patients with dizziness.

The results of the present study demonstrated that the 25-item DHI has high internal consistency for the total scale ($\alpha = .89$) and is satisfactory for the three subscales ($\alpha = .72$ to .85). As might be predicted, the total score was shown to be significantly poorer for patients reporting more frequent attacks of dizziness or unsteadiness. However, the range of total DHI scores (maximum score, 100) for the "occasionally" (0 to 50), "frequently" (12 to 60), and "continuously" (10 to 94) groups of patients with dizziness illustrates that even patients who have 12 or fewer episodes of dizziness each year may feel significantly handicapped. Alternately, patients who are continuously dizzy may not perceive themselves as being severely handicapped. This point requires further elaboration. Dizziness is one of a few disease symptoms that is capable of causing patients to modify their lives even in its absence. Thus, it is a common clinical observation that intermittent dizziness often effects changes in a patient's daily activities even during time of remission. For example, individuals may restrict their driving habits or social activities in fear of a dizziness attack.

Of particular interest were the absent correlations between dizziness handicap score and subject age. It would appear that the presence of dizziness affects the same level of handicap regardless of age. Also, it was surprising that the magnitude of self-perceived physical impairment bore no predictable relationship with the frequency of dizziness episodes. It might have been predicted that perceived physical handicap would have increased with the frequency of dizziness episodes. However, the items in the physical subscale (example: "Does bending over increase your problem?") may have been insensitive to dizziness frequency, and, therefore, even patients with occasional dizziness often answered "yes."

The DHI could be used to identify specific functional, emotional, or physical problems associated with an individual's reaction to vestibular impairment. For instance, a patient who has had two violent attacks of vertigo in a 4-year period who shows a DHI score of 96 may be referred for psychological counseling. The DHI in this case might suggest that this patient's behavior is unusual given the clinical history. In this way, a clinician's efforts could be directed toward resolving or providing information regarding adaptive techniques in the areas of concern to the patient.

Most importantly, our interest in the development of the DHI grew out of a frustration in not having adequate tools to assess the effects of treatment for dizziness. We are currently in the process of administering this scale to patients prior to and following medical, surgical, and rehabilitative treatment for dizziness and unsteadiness.

For this reason, test-retest reliability data are important. High statistically significant correlations were obtained on test-retest. These values exceeded the criteria established by Nunnally[5] in 1978 to be considered acceptable for clinical purposes ($r > .80$). Thus, changes in handicap score following therapeutic intervention would probably be due to the treatment per se, rather than to the lack of reliability of the measuring instrument if these changes exceeded a preset criterion level (eg, 95% confidence interval). Therefore, the DHI may be appropriate as a baseline measure against which treatment effects could be judged. Future investigation might entail application of the formula proposed by the committee in 1972 for evaluation of therapy for Meniere's disease[2] as well as administration of the DHI in a pretreatment and posttreatment protocol. In this way, it would be possible to evaluate the efficacy of treatment from different perspectives.

In conclusion, we have developed a self-assessment inventory that is reliable, requires little time to administer, is easy to score and interpret and, we feel, provides information that is useful for the planning and assessment of therapy. Due to the psychometric adequacy of the DHI, we believe that the scores obtained may be regarded as a criterion measure against which to document medical, surgical, or rehabilitative intervention, when used in a pretreatment and posttreatment protocol.

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Rhabdomyosarcoma of the Head and Neck in Children

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• Rhabdomyosarcoma is the most common soft-tissue sarcoma in infants and children, with the head and neck being the most frequent site of involvement. Treatment for this neoplasm has undergone many changes, with a much improved prognosis using a combination of surgery, radiation therapy, and chemotherapy. This retrospective analysis presents the management and outcome of 60 children (aged 3 months to 18 years) with rhabdomyosarcoma of the head and neck evaluated at the Children's Hospital of Philadelphia (Pa) between 1970 and 1987. The overall death rate for all head and neck sites decreased from 50% in 1970 to 1979 to 23% in 1980 to 1987, reflecting the improved management protocol.

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Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in infants and children, with the head and neck being the most frequent sites of involvement.[1-3] In the past 20 years, treatment for this malignancy has undergone many changes, and there has been a significant increase in the survival rates.[1-4] The most recently available cancer statistics compiled by the American Cancer Society reveal this improved prognosis. The relative 5-year survival rate for RMS in children under the age of 15 years has increased almost twofold, from 34% in 1967 through 1973 to 67% in 1977 through 1983.[5]

Prior to the advent of chemotherapy for RMS, the mainstay of treatment was surgical resection followed by radiation therapy, often resulting in major morbidity, and the prognosis remained poor even with this therapy.[6,7] Multiagent chemotherapy is now the standard in the treatment of RMS. Using a combination of surgery, radiation, and chemotherapy, up to 80% of children may now survive RMS with relatively little morbidity.[8] This study reviews the trends in survival since the use of multiagent chemotherapy has become a standard for the treatment of RMS.

MATERIALS AND METHODS

Between 1970 and 1987, 60 children, aged 3 months to 18 years, with RMS of the head and neck have been evaluated at the Children's Hospital of Philadelphia (Pa). A retrospective review of data collected by the Tumor Registry of the hospital was conducted. All head and neck sites were included. The information gathered on each patient included sex, race, age at presentation, histologic diagnosis, place of diagnosis, presenting symptoms, interval between symptom onset and diagnosis, tumor staging, metastatic workup, all operative procedures performed, radiotherapy and chemotherapy protocols, outcome, and follow-up.

RESULTS

There was an almost equal distribution of cases between the sexes, with 29 males and 31 females in our study. Of 60 reported cases, 10 were blacks, 1 was a Hispanic, and 48 were whites, reflecting the racial distribution of the Delaware Valley. The age distribution is shown in the Figure. More than half of the cases were diagnosed in children 6 years of age or younger. The predominant sites of presentation were the orbit and nasopharynx, each accounting for 25% of the total number of tumors (15). These sites are followed in frequency by the paranasal sinuses, 12% (7); ear, 10% (6); oral cavity including tongue, 10% (6); neck, 8% (5); parotid gland and temporalis muscle, 8% (5); and facial soft tissue, 2% (1). Table 1 lists the group at presentation following the Intergroup Rhabdomyosarcoma Study group classification.[4] There are four groups, defined as follows: group 1, localized disease, completely resected (regional nodes not involved); group 2, grossly resected tumor with microscopic residual disease; group 3, incomplete resection or biopsy with gross residual disease; and group 4, distant metastatic disease present at diagnosis. The great majority of cases were group 3 at diagnosis.

Surgical procedures varied from biopsy only to radical resection. Fifty-seven percent of the patients underwent biopsy only, 29% underwent partial removal (remaining gross disease or positive margins), 7% had a com-

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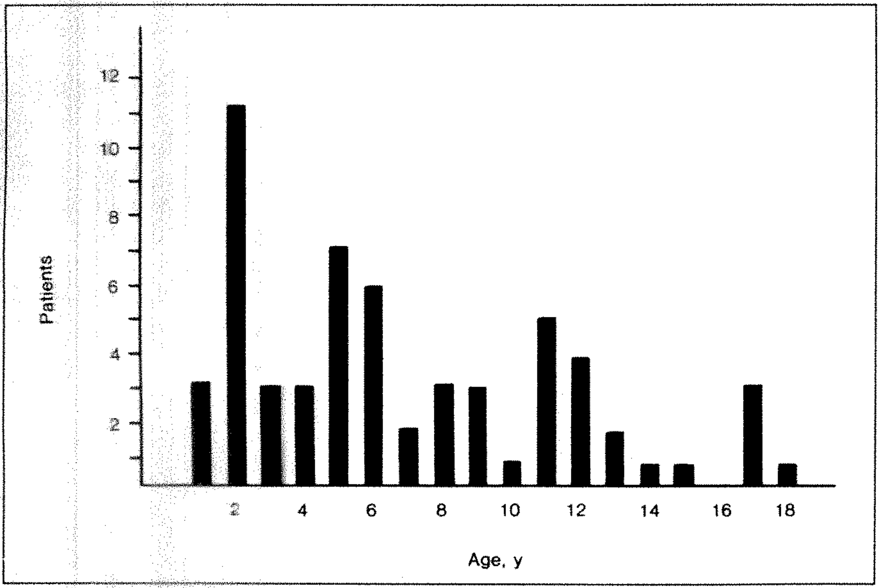

Age distribution of patients with rhabdomyosarcoma.

Table 1.—Group at Presentation*	
Group	**No.**
1	4
2	8
3	42
4	5

*Group unknown in one patient.

Table 2.—Meningeal Involvement*		
Site	**Initially**	**Total**
Orbit	...	...
Nasopharynx	...	2
Ear	1	3
Sinuses	...	1
Neck	...	...
Parotid/temporalis	...	...
Oral cavity	...	...
Total	1	6

*Meningeal involvement is defined as the presence of tumor cells identified in the cerebrospinal fluid specimen.

Table 3.—Mortality Rate	
Group	**% Mortality**
1	0
2	33
3	29
4	80

plete excision (removal of all tumor, with negative margins by histologic examination), and 7% underwent a radical resection (including removal of involved and adjacent vital structures to achieve a negative margin). Examples of procedures classified as "radical" include temporal bone resection and craniotomy with removal of the orbital roof.

Most of our cases of RMS were diagnosed in a community hospital. The initial surgery for diagnosis was performed in an outside hospital in 72% of these patients, with subsequent referral to our institution for oncologic treatment. Only 28% of the cases were diagnosed primarily at the Children's Hospital of Philadelphia.

The interval from symptom onset to diagnosis varied from 3 days to 6 months. The average interval was 35 days for orbital sites, 9 weeks for the nasopharynx, 7 weeks for the ear, and 6 weeks for the paranasal sinuses.

There are generally recognized to be four histologic subtypes of RMS: embryonal, botryoid (a variant of embryonal), alveolar, and pleomorphic. In this study, there were 36 cases of embryonal RMS, 3 alveolar, and 1 pleomorphic. The histologic subtype was not available in 20 patients. There were no cases classified as botryoid.

Patients showing meningeal involvement, as documented by tumor cells being present in the cerebrospinal fluid, are listed by site in Table 2. The parameningeal sites are defined as the nasopharynx, ear, and paranasal sinuses and carry a worse prognosis. All cases of documented meningeal involvement occurred in parameningeal tumors.

All patients reviewed in this study received multiagent chemotherapy. The most often used protocol included a combination of vincristine, cyclophosphamide, actinomycin D, and/or doxorubicin. The chemotherapeutic protocol is unknown in 1 patient.

Fifty-eight of 60 patients received radiation therapy. One patient who did not receive treatment had localized disease completely resected (group 1), and 1 patient's family refused radiotherapy. Dosages ranged from 2700 cGy to 8500 cGy (iridium implant) to the primary site. One patient with group 4 disease did not receive radiation to the primary site but did receive treatment to the metastatic sites.

Table 3 lists mortality rate by group. The highest mortality is associated with the advanced stages of this disease. In this study, mortality is approximately equal for group 2 and group 3 diseases.

To examine survival trends, the database was divided into two time periods: 1970 to 1979 and 1980 to 1987. Overall mortality in the two time periods is shown in Table 4 for the most common sites. The greatest improvement in survival is seen for tumors arising in the orbit and nasopharynx. Prognosis remains poorest for tumors arising in the ear.

Of 60 patients studied, 11 died without achieving remission of their tumor, and 11 died of a recurrence. The status of the tumor at death in 1 patient is unknown. Of 11 recurrences, 7 were local and 4 were distant. The time to local recurrence varied from 6 months to 6 years. The time to distant recurrence was shorter overall, ranging from 13 months to 3.5 years. Four patients died free of disease: 2 of heart failure secondary to doxorubicin cardiomyopathy, 1 of a secondary malignancy (acute myelocytic leukemia), and 1 of meningitis secondary to a persistent iatrogenic cerebrospinal fluid leak.

COMMENT

Rhabdomyosarcoma comprises 5% to 15% of all neoplasms in children, ranking seventh among the common malignancies of childhood.[1,2] The peak incidence is in the 2- to 5-year age group, with a second peak occurring between 15 and 19 years of age.[2] White

Table 4.—Mortality by Date

Site	1970 to 1979		1980 to 1987	
	No.	Mortality, %	No.	Mortality, %
Orbit	2/9	22	0/6	0
Nasopharynx	4/6	67	3/9	33
Ear	5/5	100	1/1	100
Sinuses	2/3	67	2/4	50
Total	15/30	50	7/30	23*

*Follow-up not available for one patient.

children are affected much more frequently than children of other races by a ratio of about 3:1.[2] Some series have shown a slight male predominance, with a male to female ratio of 1.4:1.[1,2,4]

The head and neck are the most common sites of origin, followed by the genitourinary tract, the extremities, trunk, and retroperitoneum. The embryonal form is the most common histologic subtype found in the head and neck.[2,4] Embryonal RMS is believed to arise from the primitive muscle cell, as it would be found in a 7- to 10-week fetus.[1] Cross-striations are uncommonly found in this tumor, making the histologic diagnosis more difficult. It has been estimated that up to 50% of proven cases of RMS are incorrectly diagnosed on initial biopsy.[1] Feldman[1] reviewed cases referred for consultation to the Armed Forces Institute of Pathology Otolaryngologic Tumor Registry, Washington, DC, and found the differential diagnoses included 24 different types of tumors.

When faced with a possible RMS of the head and neck, the diagnostic workup should include complete history and physical examination, complete blood cell count, chest roentgenogram, urinalysis, and blood chemistry profile, including liver enzymes. Computed tomography or magnetic resonance imaging should be performed, with particular attention to detection of bone erosion at the skull base. Radionuclide bone scans have not been shown to be reliable indicators of skull base involvement.[2] The initial surgical procedure should be adequate biopsy, with complete excision of tumor if feasible without causing excessive morbidity.

Although our data indicate that the majority of patients with RMS are being diagnosed in a community hospital, we advocate that the initial evaluation be done at a tertiary children's hospital. Fresh tissue is often needed to differentiate RMS from other small-cell tumors, and the facilities for advanced tumor marker studies are available only at these tertiary care academic centers. To make the diagnosis expeditiously and to save the child from repeated surgical procedures, we strongly believe that any patient suspected of having a childhood cancer be referred to a tertiary initial biopsy. With the availability of a pediatric oncologist in the operating room, other studies can be completed at the initial surgical procedure. If frozen section diagnosis is consistent with RMS, bone marrow aspiration and biopsy are performed during this operative setting, and when a parameningeal site is involved, the child should also undergo a lumbar puncture.

There is no indication for initial radical surgical excision if vital structures need to be sacrificed. In some instances, tumor debulking is indicated, eg, tumor necrosis in a sinus. Radical resection with sacrifice of vital structures (eg, facial nerve, globe) may be required to treat recurrent or residual disease after completion of combination therapy.

One finding of the Intergroup Rhabdomyosarcoma Study of particular interest to the otolaryngologist-head and neck surgeon is that the incidence of cervical metastases in patients with head and neck RMS is only 3%.[4] As such, prophylactic neck dissection is not currently recommended. If a neck mass is present, there is not a clear indication at present to perform a therapeutic neck dissection although this approach has been advocated.[3] Chemotherapy and radiation therapy appear to be successful in treating cervical metastases at our institution.

Rhabdomyosarcoma often presents as a relatively innocuous problem, eg, recurrent otitis media or sinusitis. For this reason, it is not uncommon for there to be a significant delay in diagnosis of this tumor. In our series, the average interval between symptom onset and diagnosis was 6 weeks, being longest for tumors arising in the nasopharynx and shortest for orbital tumors. The orbital masses are probably brought to the attention of the physician sooner because of their visibility.

The parameningeal sites (ear, nasopharynx, sinuses) often initially present with nasal discharge, otitis media, and headache. Since these parameningeal tumors often present with signs and symptoms of other common conditions, we do not believe that earlier diagnosis is feasible. Both serous otitis media and sinusitis are common in children, so a several-week course of antibiotics is medically and economically sound treatment. One would not advocate performing computed tomography or magnetic resonance imaging on all children presenting with sinusitis or recurrent otitis media to rule out RMS. Certainly, when the presentation includes cranial nerve dysfunction, suspicion of a malignant process should be high, and appropriate workup should be instituted immediately. We have not noticed a substantial shortening of time to diagnosis over the 17-year period of this study. Even with advanced imaging techniques, the common symptom presentation of many RMS of the head and neck makes a delay in diagnosis inevitable. As many as 35% of these patients with tumor in parameningeal locations exhibit direct tumor spread into the central nervous system.[9] Chemotherapy regimens, including intrathecal therapy, are currently inadequate for treating meningeal involvement.[1]

The first article on the combination of surgery, radiation, and chemotherapy for the treatment of RMS was in the early 1960s.[10] Chemotherapy has been successful in causing both shrinkage of the primary tumor and control of metastatic disease. Radiation therapy is used primarily for local control.[1] The current recommendation is for 5000 to 6000 cGy to the primary site in children over 3 years of age. In younger children, 4000 to 4500 cGy are administered. Up to 4000 cGy can be delivered to the brain. The radiation is delivered on a daily basis for 5 to 6 weeks.[11]

At our institution, our approach is as follows: if the tumor is localized and can be excised completely or with only microscopic residual disease (clinical group 1 or 2), without untoward disability or mutilation, such surgery is performed. Patients then receive chemotherapy with vincristine and actinomycin D for 1 year, with radiation therapy added for group 2 patients. Patients whose tumors are not resectable or are disseminated (clinical groups 3 and 4) begin intense chemotherapy as soon as the diagnostic evaluation is completed. The drugs and schedules used vary according to the current Intergroup Rhabdomyosarcoma Study regimens, but currently include combinations of vincristine, actinomycin D, cyclophosphamide, ifosphamide, etoposide, doxorubicin, and melphalan. "Second-look" surgery is sometimes performed to monitor the effects of chemotherapy histologically, or to excise a tumor that has become amenable to surgery. Radiation therapy begins concurrently with chemotherapy when there is evidence of central nervous system or cranial nerve involvement; otherwise it begins after 6 to 9 weeks of chemotherapy.

In this study, we found a slightly higher mortality rate for our group 2 patients and a lower mortality rate for group 3 patients than is generally reported.[1,2,8] One third (4/12) of our group 2 patients died. Three of these patients suffered local recurrences after being successfully treated. One patient developed acute myelocytic leukemia after being tumor free for over 4 years, and her death was secondary to the leukemia. Recurrences in RMS carry a grave prognosis.[3] In our study, no child with a recurrence, either local or distant, has survived despite intensive re-treatment.

Our improved survival of group 3 patients is related in part to the large number of patients with orbital RMS in this group (13/42). Orbital tumors carry a better prognosis, perhaps because they are detected earlier than RMS at other sites. If we exclude the orbital sites from our group 3 patients, the mortality increases from 29% to 41%.

Since the use of combination therapy, we have noted a continuing improvement in survival in children with head and neck RMS. Some of this apparent improvement over time may be due to inadequate follow-up, as the patients reviewed during the time frame 1980 to 1987 have had a shorter follow-up time (mean, <3 years) than those in the preceding decade. However, we believe that the improved survival rate is real. We believe that the marked improvement in survival is most probably due to better supportive care of patients during more intensive radiation and chemotherapy. The use of hyperalimentation to maintain nutrition has been a major factor in prolonging survival. Improved antibacterial and antifungal medications have also contributed to improved survival.

In the management of RMS of the head and neck, close communication and cooperation among the otolaryngologist, oncologist, and radiation therapist are essential. The goal of the initial surgery is to obtain complete resection of the tumor if this does not sacrifice vital structures or function. Chemotherapy and radiation therapy are the primary treatment modalities of RMS, and with the improvement in supportive care of these patients during their intensive combination therapy, survival rates have improved significantly during this past decade.

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Patterns of Cervical Node Metastases From Squamous Carcinoma of the Larynx

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• We undertook a retrospective review of 247 previously untreated consecutive patients from 1965 to 1986 with primary squamous cell carcinoma of the supraglottic or glottic larynx to ascertain the prevalence of neck node metastases by neck level. The 247 patients underwent a total of 262 radical neck dissections. Patients were grouped by clinical neck status at the time of neck dissection: elective dissection in the N0 neck; immediate therapeutic dissection in the N+ neck; and subsequent therapeutic dissection in the N0 neck that over time converted clinically to N+. Detailed analysis revealed a predominance of neck node metastases in levels II, III, and IV for all clinical neck groups. Level V was rarely involved, but always in conjunction with neck node metastases in levels II, III, or IV (ie, N2 disease). Level I was rarely involved; involvement occurred with neck node metastases in levels II, III, or IV 75% of the time. Level I involvement correlated with T3 or T4 primary tumors exhibiting histologic extralaryngeal spread. These data support the trend toward selective limited neck dissection in both N0 and N1 patients.

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The extent of cervical lymphadenectomy for squamous cell carcinoma of the larynx remains controversial. Radical neck dissection, since its description by Crile[1] in 1906, has been the traditional approach for excision of cervical metastases in the neck. This operation offers comprehensive clearance of neck levels I through V (Fig 1). More recently, modifications in the extent of lymphadenectomy, especially in the N0 and N1 patient, have been championed by Bocca et al[2] and Byers et al.[3,4] No prospective, randomized comparison between radical neck dissection and selective limited neck lymphadenectomy in laryngeal squamous cell carcinoma has been conducted. In preparation for such comparison trials, we present retrospective data to demonstrate the prevalence and patterns of regional lymph node metastases from primary laryngeal squamous cell carcinoma in a series of patients, all of whom underwent classic radical neck dissections.

MATERIALS AND METHODS

From the beginning of 1965 through the end of 1986 there were 785 patients with laryngeal carcinoma registered on the Head and Neck Service at Memorial Sloan-Kettering Cancer Center, New York, NY. A retrospective review of the pathology reports of 247 previously untreated consecutive patients from this group was undertaken to ascertain the prevalence and distribution of neck node metastases by neck level. All of these patients had complete radical neck dissections. The remaining 538 patients were excluded because they did not have a neck dissection or had a modified neck dissection, multiple primary sites, preoperative chemotherapy, or preoperative radiation therapy. Only 6 patients had subglottic or transglottic disease, and they were omitted from analysis because of the small sample size.

There were 262 radical neck dissections in the 247 patients. In 15 patients (6%), a simultaneous bilateral neck dissection was performed. In 207 dissections (79%), the exact count of lymph nodes pathologically examined was reported, and was 37 on average. In the remaining 21% of patients, lymph node counts were reported as "numerous," "matted," or "multiple" for one or more levels. Patients were considered to have nodal disease and counted as having a positive level when one or more nodes were reported to contain tumor.

Patients were grouped by clinical neck status at the time of neck dissection (Fig 2). The three clinical groups were (1) elective dissection in the clinically N0 neck (n = 78); (2) immediate therapeutic dissection in the clinically N+ neck (n = 118); and (3) subsequent therapeutic dissection in the patients whose clinical status progressed to N+ during observation (n = 51). Subgroups were formed for each clinical group and analyzed by specific primary site: supraglottic larynx (n = 189) or glottic larynx (n = 58).

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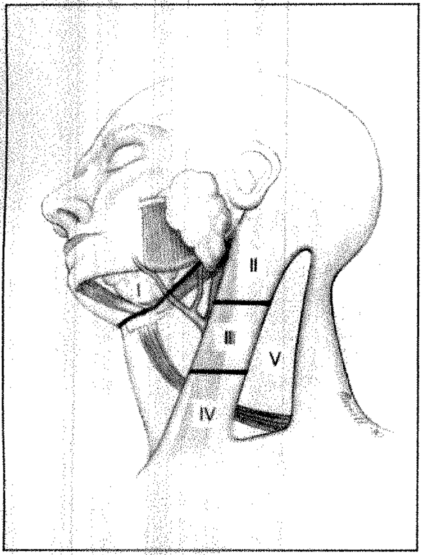

Fig 1.—Cervical lymph node levels used for description of clinical and pathologic findings.

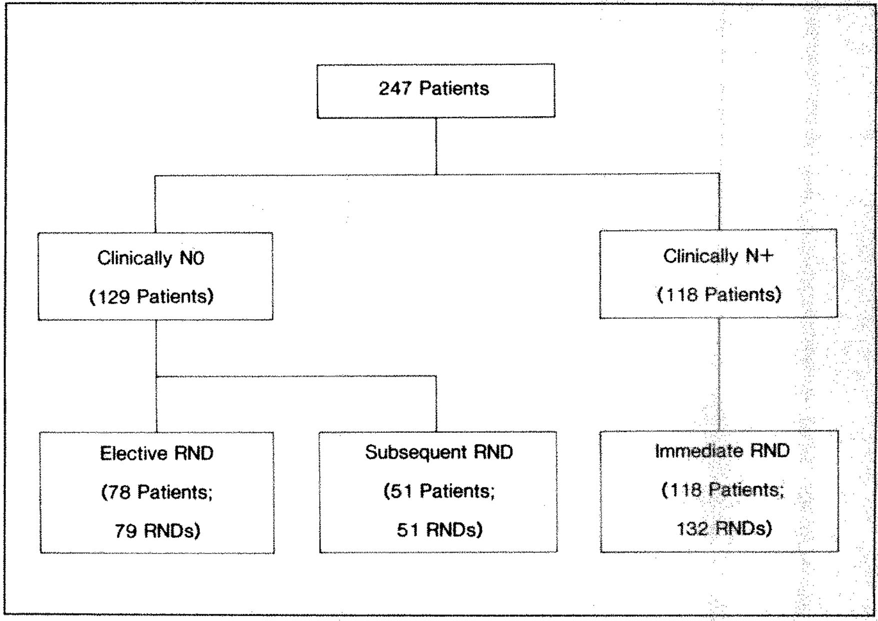

Fig 2.—Distribution by clinical N status at first presentation. RND indicates radical neck dissection.

Table 1.—Population Distribution by Clinical Stage

Stage	No. (%) of Patients
I	6 (2.5)
II	52 (21)
III	129 (52.5)
IV	60 (24)
Total	**247 (100)**

Table 2.—T Stage by Clinical Groups*

	No. of Patients		
T Stage	Elective RND, N0 (n = 78)	Immediate RND, N+ (n = 118)	Subsequent RND, N+ (n = 51)
1	3	7	2
2	33	49	20
3	34	46	29
4	8	16	0

*RND indicates radical neck dissection.

Table 3.—Prevalence of Nodal Metastases by Neck Level*

	No. (%) of Patients		
Neck Level	Elective RND (n = 79)	Immediate RND (n = 132)	Subsequent RND (n = 51)
I	4 (5)	8 (6)	4 (8)
II	15 (19)	81 (61)	24 (47)
III	16 (20)	71 (54)	37 (73)
IV	7 (9)	39 (30)	16 (31)
V	2 (2.5)	8 (6)	0
Group prevalence	29 (37)	111 (84)	44 (86)

*RND indicates radical neck dissection.

Compilation of data was performed using the DBase III-Plus program (Ashton-Tate, Torrance, Calif). Statistical analysis was performed using the χ^2 technique.

RESULTS

The population of 247 patients was composed of 190 men (77%) and 57 women (23%). Age ranged between 20 and 78 years, with a mean of 59 years and a median of 60 years. The population distribution by clinical stage is shown in Table 1. The T stage for each clinical group is shown in Table 2.

N0 Neck (Elective Radical Neck Dissection)

Seventy-eight patients who were N0 at presentation underwent 79 immediate elective radical neck dissections. Sixty-four patients had supraglottic and 14 had glottic primary sites. One patient with a supraglottic primary site underwent simultaneous bilateral neck dissections. Breakdown by clinical T stage is shown in Table 2. Clinically occult, metastatic squamous cell carcinoma was present in 29 (37%) of the 79 dissections. The overall prevalence of nodal metastases by neck level is shown in Table 3. Neck level I nodes were rarely involved, occurring in the supraglottic subgroup in 4 (5%) of 79 dissections as shown in Table 4. Of the two patients with level V involvement, both had nodal metastases at other levels.

N+ Neck (Immediate Therapeutic Radical Neck Dissection)

There were 132 radical neck dissections in 118 patients who presented with a clinically N+ neck. One hundred six patients had supraglottic and 12 had glottic primary sites. Thirteen patients with supraglottic primary sites had bilateral neck dissections. In 5 patients, the side of the neck contralateral to the primary site was the side clinically N+ and dissected. One patient with a glottic primary had a bilateral neck dissection. Clinical T stage is shown in Table 2. Eighty-four percent (111 of 132) of dissections had nodal metastatic disease confirmed histologically. The prevalence of nodal metastatic disease by neck level is shown in Table 5. Overall, level I was only slightly more commonly involved in patients with nodal metastases (6%) than in the clinically N0 patients (5%) due to a 15% prevalence in the glottic subgroup (Table 5). Of the 8 patients with level V nodal metastases, all patients had nodal metastases in other levels (Table 5).

Table 4.—Prevalence by Primary Site: Elective N0 Radical Neck Dissection (n = 79)

	No. (%) of Patients	
Neck Level	Supraglottic (n = 65)	Glottic (n = 14)
I	4 (6)*	0
II	12 (18)	3 (21)
III	12 (18)	4 (29)
IV	6 (9)	1 (7)
V	1 (1.5)†	1 (7)†
Group prevalence	24 (37)	5 (36)

*Three of these four had metastases at other levels.

†Both of these patients had metastases at other levels.

Table 5.—Prevalence by Primary Site: Immediate N+ Radical Neck Dissection (n = 132)

	No. (%) of Patients	
Neck Level	Supraglottic (n = 119)	Glottic (n = 13)
I	6 (5)*	2 (15)†
II	74 (62)	7 (54)
III	63 (53)	8 (61)
IV	37 (31)	2 (15)
V	7 (6)†	1 (8)†
Group prevalence	102 (86)	9 (69)

*Three of these six had metastases at other levels.

†All of these patients had metastases at other levels.

Table 6.—Prevalence by Primary Site: Subsequent Radical Neck Dissection (n = 51)

	No. (%) of Patients	
Neck Level	Supraglottic (n = 19)	Glottic (n = 32)
I	2 (11)*	2 (6)*
II	12 (63)	12 (38)
III	13 (68)	24 (75)
IV	7 (37)	9 (28)
V	0	0
Group prevalence	18 (95)	26 (81)

*All of these patients had metastases at other levels.

N+ Neck (Subsequent Therapeutic Radical Neck Dissection)

Fifty-one radical neck dissections were performed in 51 patients initially staged N0 who subsequently developed an N+ neck. Nineteen patients had supraglottic and 32 had glottic primary sites. In 5 patients with glottic primary sites, the contralateral side of the neck converted to N+ and was dissected. Clinical T stage is shown in Table 2. In this N+ group, 86% of dissected necks (44 of 51) had nodal metastatic disease. The prevalence of nodal metastatic disease by neck level is shown in Table 3. Level I was involved in 11% and 6% of supraglottic and glottic site subgroups, respectively (Table 6). All 4 patients with level I nodal metastases had metastases in other levels. No patient with a supraglottic or glottic primary site had level V involvement in this group (Table 6).

The overall sensitivity, specificity, and accuracy of the clinical examination of the neck was 79%, 70%, and 76%, respectively. There was no statistically significant difference in the prevalence of nodal metastatic disease, in any neck level, between supraglottic and glottic primary sites when analyzed within each major clinical group.

COMMENT

The classic approach for the surgical treatment of neck node metastases has been a radical neck dissection. Since its description by Crile[1] in 1906, and following its routine practice by Hayes Martin and others, it has become the mainstay of surgical treatment for decades. More recently, Bocca et al[2] and Byers et al[3,4] have suggested modification of the standard dissection technique to avoid its attendant morbidity. Bocca et al and others base their beliefs on anatomic studies demonstrating the whole lymphatic system of the neck to be contained within an aponeurotic envelope.[5-7] By detaching this envelope from underlying vital structures, lymph nodes and lymphatic channels can be extirpated without sacrifice of other major neck structures. Bocca et al believe adequate "cancerologic radicality" can be achieved by a functional neck dissection. Indeed, recurrence rates were similar when they compared results of their functional neck dissections with those in historic controls undergoing radical neck dissection.[2]

Support is now mounting for a similar approach to patients with limited nodal metastases (N1) at first presentation.[8-11] Byers et al, in several retrospective studies from the M. D. Anderson Hospital, Houston, Tex, have demonstrated the modified neck dissection(s) to be adequate therapy for N0 or N1 necks. Further, they advocate an anterior neck dissection (containing cervical nodal levels II, III, and IV) for primary tumors of the larynx (and oropharynx) in selected N0 or N1 patients. They state that the submandibular triangle need not be dissected, since the nodes were not found to be at risk. The data they use in support of their conclusions is based on a relatively large number of patients who underwent modified neck dissections. Further, they found no statistically significant difference in recurrence rates between groups of patients, pathologically N0 or N1, in whom anterior neck dissection was performed, with or without adjuvant radiation therapy.

We believe our retrospective study to be unique in that it represents a large number of patients with primary laryngeal squamous cell carcinoma, *all of whom underwent radical neck dissection*. Thus, detailed pathologic analysis of all cervical lymph node levels was available in all patients. Our reported node counts averaged six nodes more per patient than Byers et al obtained with functional neck dissection.

It is important to stress that our study deals with nodal metastases only. Since all nodal groups were excised in all patients, the question of neck failure rates beyond the dissected nodal groups does not arise. Further, only selected N0 patients were treated with radical neck dissection. Clearly, the exact reason for neck dissection in these N0 patients is unknown. Presumably, they represented patients believed to be at increased risk of harboring micrometastases.

In our clinically N0 patients, if an anterior neck dissection had been performed instead of a radical neck dissection, six patients (7.6%) would have had nodal metastases left behind: four in level I and 2 in level V (Table 4). Only one patient with level I nodal metastases had isolated level involvement outside of level II, III, or IV. This patient represents only 1.2% of the whole N0 group, and is the only patient with a skip metastasis outside the borders of an anterior neck dissection.

This patient had a T4 primary tumor demonstrated by soft-tissue infiltration on histologic review. The other three patients with level I disease were N2 pathologically.

Clearly, an anterior neck dissection would have removed the majority of lymph nodes harboring occult metastases in our N0 or pathologically N1 patients. Overall, the 7.6% of patients with nodal disease outside levels II, III, or IV parallels the 8% incidence of local recurrence reported by Byers[3] in pathologically N0 patients undergoing anterior neck dissection for laryngeal or hypopharyngeal primary sites.

If an anterior neck dissection had been performed on our clinically N+ patients, we would have left nodal metastases in 12 patients at level I and 8 patients at level V (Tables 5 and 6). Level V was never pathologically involved in the absence of nodal disease at other levels. Only 3 (15%) of the 20 patients had isolated level involvement outside the boundaries of an anterior neck dissection. All three patients had isolated level I involvement. One patient had a T4 primary tumor with extension to the base of the tongue. The second had a T3 primary tumor with perforation of the larynx and invasion into the soft tissues. The third patient had a T2 primary tumor that was histologically poorly differentiated. Further analysis of all patients with level I involvement revealed that 75% (12 of 16) of patients had evidence of extralaryngeal spread when their primary tumors were reexamined histologically. Overall, the most common sites of extralaryngeal spread were the soft tissues of the neck (five cases) and the base of tongue (three cases).

CONCLUSION

Based on this series of 247 patients undergoing 262 radical neck dissections, we found neck levels II, III, and IV to be at greatest risk of nodal metastases from primary squamous cell carcinoma of the larynx. Level I was rarely involved in the clinically N0 (5%) and N+ patients (7.8%). Likewise, neck level V was rarely involved in the N0 (2.5%) and N+ (4.4%) groups. Level V involvement was *always* associated with nodal metastases at other neck levels (ie, N2 disease).

The relative merit of modified neck dissection vs radical neck dissection in patients with laryngeal squamous cell carcinoma cannot be determined by our data. We feel our data support but do not prove the current trend toward effectiveness of modified neck dissection in both N0 and N1 patients. Specifically, an anterior dissection for N0 and N1 necks should remove the majority of nodal metastases. Ideally, identification of positive nodes in the operating room would alert the surgeon to the potential of nodal disease in levels I or V. Unfortunately, this cannot be achieved with acceptable sensitivity. During surgery, however, we can reliably identify patients with extralaryngeal spread of the primary tumor.[12]

We believe patients with supraglottic carcinoma and evidence of extralaryngeal spread of the primary tumor (either grossly or on frozen section) should have level I dissected. Further, any patient with evidence of N2 nodal disease at the time of operation should undergo a comprehensive functional or radical neck dissection to ensure removal of all nodes at risk.

Clearly, prospective, randomized trials comparing the morbidity and neck recurrence rates in patients with laryngeal squamous cell carcinoma undergoing modified neck dissection vs classic radical neck dissection are indicated.

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Tumor Necrosis Factor and Cytotoxic Agents

Effect on Squamous Carcinoma Lines

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• The cytotoxicity of dactinomycin (actinomycin D), doxorubicin hydrochloride (Adriamycin), cisplatin, fluorouracil, and methotrexate alone and in combination with recombinant human tumor necrosis factor (rHuTNF) on human squamous cell carcinoma lines was studied by an MTT proliferation assay. The rHuTNF alone caused no inhibition after 24 to 72 hours. All lines investigated showed a dose-dependent response to dactinomycin and doxorubicin. Potentiation of dactinomycin and doxorubicin cytotoxicity occurred with four of six cell lines following incubation of rHuTNF and the drug. No synergistic effect on cytotoxicity was seen with rHuTNF and any chemotherapeutic agent on two cell lines. The addition of rHuTNF did not augment the cytotoxic effect seen with cisplatin, methotrexate, or fluorouracil on any cell line. These results show that rHuTNF can enhance the cytotoxic effect of certain chemotherapeutic agents on squamous cell lines in vitro.

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Endotoxin-induced hemorrhagic tumor necrosis was first described in 1893 by Dr William Coley[1] who treated 10 patients with malignant tumors by repeated inoculations of erysipelas toxin. In 1975, Carswell et al[2] successfully isolated a serum factor from bacillus Calmette-Guérin-infected mice treated with endotoxin. This substance, which the authors called "tumor necrosis factor (TNF)," mimicked the tumor necrotic action of endotoxin, causing selective cytotoxic effect on transplantable tumors in mice. Recently, TNF was shown to be a product of mononuclear phagocytes, and it is copiously released by macrophages after exposure to lipopolysaccharide.[3] It is of great interest because TNF has proved to be cytotoxic and cytostatic for a variety of murine and human tumor cells in vitro and in vivo, while sparing normal cells.[4,5] Moreover, it has been shown that tumoricidal TNF activity can be significantly increased by addition to the culture medium of topoisomerase II-targeted cytotoxic agents.[6,7] There is little information in the literature, however, on the efficacy of TNF against squamous carcinoma or other epithelial tumors. Recently, Zenner and Zimmerman[8] found an inconsistent antiproliferative effect of TNF on cultured squamous carcinoma cells with some cell lines being susceptible, while others were not. The effect of recombinant human tumor necrosis factor (rHuTNF) on human squamous cell carcinoma (SCCa) lines of head and neck origin and its interaction with other cytotoxic agents are evaluated in this study.

MATERIALS AND METHODS

Reagents

Recombinant human tumor necrosis factor (TNF-α) was obtained, and the following chemotherapeutic agents were used: dactinomycin (actinomycin D), doxorubicin hydrochloride (Adriamycin), methotrexate, fluorouracil, and cisplatin.

Cell Lines

Human squamous cell carcinoma lines derived from the hypopharynx (FaDu), larynx (HEp-2), and oral cavity (KB-17) were obtained, as were cell lines from the supraglottic larynx (UM-SCCa 5) and oral cavity (UM-SCCa 8 and UM-SCCa 25). Cells were maintained in 25 cm^2 or 75 cm^2 tissue culture flasks (Falcon Plastics, Cockeysville, Md) with RPMI 1640 medium containing 15% fetal calf serum, antibiotics, and supplements (University of Iowa Cancer Center, Iowa City) in a 5% CO_2, 97% humidity, and 37°C environment.

MTT Cytotoxicity Assay

Squamous cells in the exponential phase of growth were harvested from culture flasks using 0.1% trypsin and 0.4% edetic acid (EDTA) (University of Iowa Cancer Center). The cells were washed in medium, counted via hemocytometer, and their viability was determined by 0.5% trypan blue vital dye exclusion. Only harvested aliquots showing viability of greater than 90% were used in these studies. The cells were then transferred to 96-well microtiter plates (Falcon Plastics) at 100 000 cells per well in 0.1 mL of medium. Preliminary studies demonstrated that this number of cells was not confluent at the end of the assay and provided an optimal MMT absorbance value. The cells were allowed to adhere for 24 hours in 5% CO_2 at 37°C. The medium was then replaced and various concentrations of cytotoxic agents, with or without rHuTNF, were added; final volume was 0.2 mL. The plates were incubated for 24 hours at 37°C in 5% CO_2 and cell viability in each well was estimated via the colorimetric MTT assay according to the method of Mosmann.[9] The yellow tetrazolium salt MTT (3[4,5-dimethylthiazol-2-yl] 2,5-diphenyl-tetrazolium bromide, Sigma Chemicals, St Louis, Mo) is converted into a purple formazan product by living cells in direct proportion to cell number and metabolic activity.[9] Briefly, 5 μL of a 10-mg/mL solution of MTT in phosphate-buffered saline (0.01 mol/L of PO_4, 0.85% NaCl, at a pH of 7.4) was added to each well and incubated for 4 hours at 37°C. The content of each well was then solubilized by addition of 0.175 mL of acid isopropanol (0.4N HCl in 2-propanol) at room temperature, and absorbance of each well was measured at 570 nm by a multiple scanning spectrophotometer (Bio-Tek Instruments, Winooski, Vt). The percent viability of each well was determined from the absorbance readings at 570 nm and calculated from the following: percent viability = [(drug ± rHuTNF)/control cells alone] × 100, where *drug ± rHuTNF* = mean absorbance as determined by the MTT assay with chemotherapeutic agent alone or with rHuTNF plus chemotherapeutic agent; and *control cells alone* = mean absorbance as determined by the MTT assay without chemotherapeutic agents or rHuTNF. Data are means from four replicate wells and three separate experiments. Microscopic inspection of the wells revealed that decreased absorbance values from control wells correlated with decreased cell number and not with dimin-

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ished metabolic rate.[9] Previous studies have shown that the MTT assay correlates with tritiated thymidine assays of proliferation and viability determined by propidium iodide staining using flow cytometry.[9] Also, it has been easily adapted to SCCa lines.[10]

Table 1.—Percent Viability of Cells Incubated 24 Hours With and Without Chemotherapeutic Agents and rHuTNF*

Agents, Concentration	Cell Lines SCCa 8	 SCCa 25	 FaDu	 KB-17	 HEp-2	 SCCa 5
rHuTNF, 75 ng/mL	101 ± 2.4	101 ± 1.9	106 ± 4.8	94 ± 1.4	92 ± 1.4	98 ± 0.4
Doxorubicin hydrochloride, 2.5 mg/L	76 ± 2.0†	62 ± 1.3†	73 ± 2.3‡	43 ± 1.0†	94 ± 2.9	81 ± 8.5
Doxorubicin + rHuTNF	48 ± 5.1†	49 ± 1.8†	56 ± 3.7‡	14 ± 0.6†	94 ± 2.2	81 ± 13.6
Dactinomycin, 0.25 mg/L	45 ± 1.7†	60 ± 2.3‡	58 ± 3.6†	44 ± 7.4†	95 ± 9.7	71 ± 5.6
Dactinomycin + rHuTNF	21 ± 4.0†	48 ± 1.9‡	40 ± 1.2†	11 ± 1.9†	94 ± 5.6	70 ± 5.7
Methotrexate, 2.5 mg/L	93 ± 3.0	89 ± 2.6	76 ± 6.1	83 ± 8.9	92 ± 6.5	80 ± 5.9
Methotrexate + rHuTNF	93 ± 1.9	91 ± 3.5	88 ± 3.1	84 ± 4.4	87 ± 10.8	84 ± 3.0
Cisplatin, 2.5 mg/L	93 ± 4.4	98 ± 0.7	91 ± 18.9	97 ± 2.6	97 ± 1.8	95 ± 7.6
Cisplatin + rHuTNF	95 ± 4.4	103 ± 1.5	95 ± 6.7	96 ± 3.9	92 ± 2.7	97 ± 3.9
Fluorouracil, 37.5 mg/L	91 ± 1.7	68 ± 3.6	91 ± 6.1	81 ± 3.8	83 ± 1.9	64 ± 2.1
Fluorouracil + rHuTNF	95 ± 4.1	85 ± 3.9	93 ± 2.6	79 ± 3.8	82 ± 5.9	69 ± 1.3

*Results expressed as mean cell viability with SD; rHuTNF indicates recombinant human tumor necrosis factor. Percent viability as calculated from: percent viability = [(drug ± rHuTNF)/control cells alone] × 100, where *drug ± rHuTNF* = mean absorbance as determined by the MTT assay with chemotherapeutic agent alone or in combination with rHuTNF; and *control cells alone* = mean absorbance as determined by the MTT assay without chemotherapeutic agents or rHuTNF.

†Equals significance at $P < .001$ level by analysis of two means.

‡Equals significance at $P < .01$ level by analysis of two means.

RESULTS

Recombinant human tumor necrosis factor alone at concentrations ranging from 3.125 to 200 ng/mL showed no significant cytotoxic effect after 24 hours of continuous incubation with all tested SCCa lines (Table 1). The top row of Table 1 displays cell viabilities of 92% to 106% of control wells despite continuous incubation with rHuTNF. Continuous incubation with rHuTNF as long as 72 hours failed to show any decreased viability in any line studied (data not shown). The two antitumor antibiotic drugs, doxorubicin hydrochloride and dactinomycin, were evaluated at concentrations ranging from 0.6 to 10 mg/mL for doxorubicin hydrochloride and 0.06 mg/L to 1 mg/mL for dactinomycin. Cell lines UM-SCCa 5, UM-SCCa 8, UM-SCCa 25, KB-17, and FaDu all showed prominent cytotoxicity following exposure to both of these drugs. The cytotoxic response was concentration dependent with maximal cytotoxicity seen at the highest drug concentrations as illustrated by Figs 1 and 2. Table 1 shows the cytotoxic effect of chemotherapeutic drugs on squamous carcinoma cells at concentrations near serum drug levels found during clinical use of these agents.

Incubation with doxorubicin hydrochloride at a clinically achievable concentration of 2.5 mg/L or dactinomycin at a clinically achievable concentration of 0.25 mg/L caused significant cytotoxicity in four of six cell lines (UM-SCCa 8, UM-SCCa 25, FaDu, and KB-17), while two lines (HEp-2 and UM-SCCa 5) showed little effect at these concentrations (Table 1). Higher drug concentrations were investigated with all lines studied (Figs 1 and 2). Those drug concentrations studied in combination with rHuTNF were selected to allow a level of cell viability (approximately 50% to 90%) that would demonstrate any possible drug-cytokine synergism. Incubation with therapeutic concentrations of dactinomycin and doxorubicin for 48 hours proved lethal to nearly all cells of lines UM-SCCa 5, UM-SCCa 8, UM-SCCa 25, KB-17, and FaDu, with cell viability ranging from 10% to 20%. Little cytotoxicity was observed on any of the six cell lines tested after 24 hours of continuous incubation with methotrexate, cisplatin, or fluorouracil at therapeutic concentrations (Table 1).

When rHuTNF was incubated with doxorubicin or dactinomycin, cell lines UM-SCCa 8, UM-SCCa 25, FaDu, and KB-17 showed a significant synergistic enhancement of cytotoxicity (Table 1). The cytotoxicity with these cell lines increased 20.9% to 74.5% with dactinomycin and rHuTNF, and 21.2% to 67.2% with doxorubicin and rHuTNF. The potentiation of cytotoxicity with rHuTNF and the two antitumor antibiotics was dose dependent for both drug and rHuTNF. This is illustrated by the downward sloping dose-response curves in Fig 1 when doxorubicin and dactinomycin were incubated with UM-SCCa 8 cells. Similar dose-response curves to Fig 1 were obtained with UM-SCCa 25, FaDu, and KB-17 lines (data not shown). In contrast, UM-SCCa 5 and HEp-2 squamous cell lines failed to demonstrate any significant synergism as seen by the horizontal alignment of the dose-response curves for UM-SCCa 5 in Fig 2. Similar dose-response curves were obtained for the HEp-2 cell line (data not shown). Table 2 shows the marginal augmentation of cytotoxicity, between 0.1% and 2.3%, seen with both drug and rHuTNF in these two cell lines.

The most commonly employed chemotherapeutic agents for SCCa of the head and neck, methotrexate, cisplatin, and fluorouracil, were also evaluated for synergistic cytotoxicity with rHuTNF. All failed to show any augmented cytotoxicity when combined with rHuTNF on any of the cell lines used in this study (Tables 1 and 2).

COMMENT

The purpose of this study was to evaluate the effect of rHuTNF exposure alone and in combination with other chemotherapeutic agents on SCCa of head and neck origin. It demonstrated a marked dose-dependent synergistic cytotoxicity between rHuTNF and the two antitumor antibiotic agents, doxorubicin and dactinomycin, on four squamous cell lines (UM-SCCa 8, UM-SCCa 25, FaDu, and KB-17), while two lines (UM-SCCa 5 and HEp-2) failed to show any significant potentiation. Other investigators have shown that some cells (HL-60 and L929) that were relatively resistant to the cytotoxic effects of TNF became markedly sensitive in the presence of rHuTNF to even low concentrations of

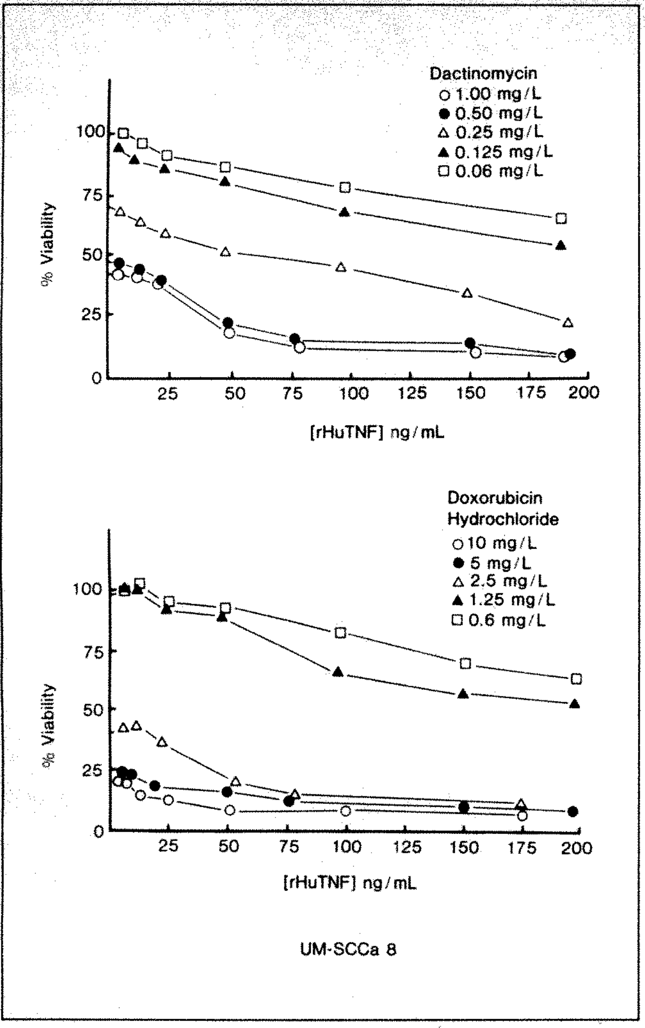

Fig 1.—Cell viability after 24 hours of incubation with recombinant human tumor necrosis factor (rHuTNF) alone or with dactinomycin (top) and doxorubicin hydrochloride (bottom) on squamous cell carcinoma (SCCa) line UM-SCCa 8. The ordinate displays percent cell viability as determined by the colorimetric MTT assay (see "Materials and Methods"). The abscissa displays concentration of rHuTNF in nanograms per milliliter. The downward sloping curves demonstrate dose-dependent cytotoxic synergism of rHuTNF with these two agents. Similar curves were obtained with cell lines UM-SCCa 25, FaDu, and KB-17.

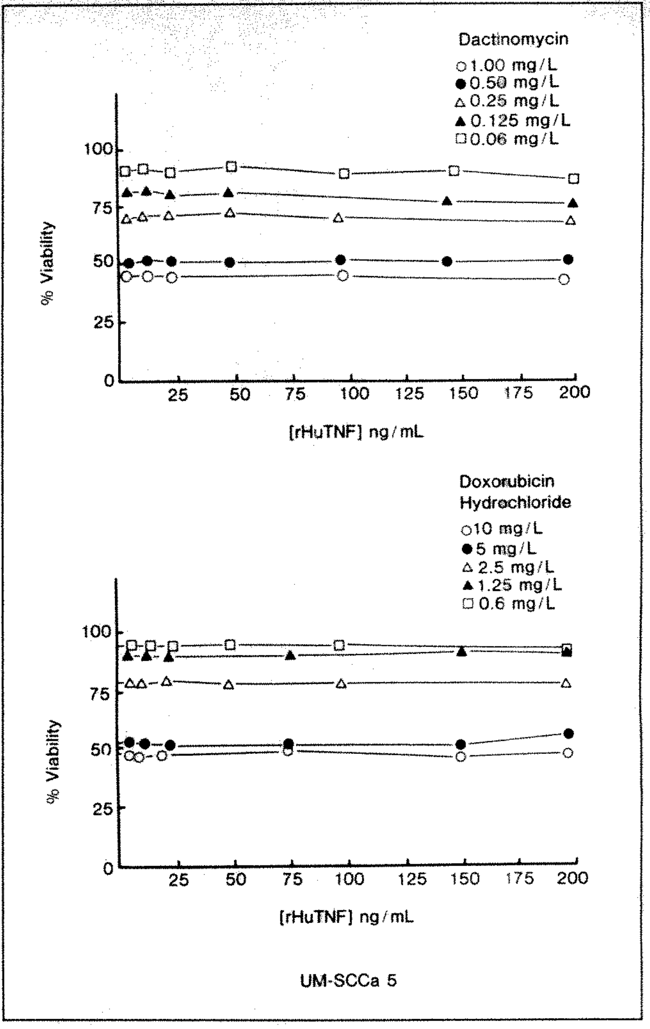

Fig 2.—Cell viability after 24 hours of incubation with recombinant human tumor necrosis factor (rHuTNF) alone or with dactinomycin (top) and doxorubicin hydrochloride (bottom) on squamous cell carcinoma (SCCa) line UM-SCCa 5. The ordinate displays percent cell viability as determined by the colorimetric MTT assay (see "Materials and Methods"). The abscissa displays concentration of rHuTNF in nanograms per milliliter. The horizontal alignment of these curves demonstrates a dose-dependent cytotoxic response to these antitumor antibiotics and no synergism with rHuTNF. Similar curves were obtained with cell line HEp-2.

dactinomycin or doxorubicin.[6,7] Significant cytotoxic synergism between rHuTNF and a number of topoisomerase II–targeted agents (dactinomycin, doxorubicin, etoposide, teniposide, and 4-[9-acridinylamino]-methanesulfon-m-anisidide) has been shown on murine fibrosarcoma cell line L929, which was otherwise not susceptible to cytotoxic effect of rHuTNF.[7] Preincubation with topoisomerase II–targeted agents for 7 and 20 hours prior to exposure to rHuTNF was shown to render the L929 cells more susceptible to the effects of rHuTNF than simultaneous incubation with cytokine and drug.[7] In the current study, attempts to demonstrate a similar modulation of the SCCa cell line susceptibility by pulsing the cells with drugs prior to rHuTNF exposure failed to augment cytotoxicity in any experiment (data not shown).

A rapid, reproducible, cost-effective, nonradioactive assay for cytotoxicity was adapted to use with the adherent SCCa cells in these experiments. Previous studies and preliminary experiments showed that dead cells did not cleave MTT to the colored formazan product measured in this assay.[9] Absorbance values at 570 nm were in direct correlation with viable cell number.[9] This assay shows promise for application to chemosensitivity testing of fresh tumor explants from patients with head and neck cancer. The lack of a reliable, rapid assay system has hindered the development of this modality for patients with SCCa.

Data in the literature on the effect of TNF on human squamous cells are very sparse. Zenner and Zimmerman[8] investigated the effect of rHuTNF on squamous carcinoma cell culture lines from larynx, submandibular, and parotid glands. These investigators ob-

Table 2.—Percent Augmentation of Cytotoxicity by Incubation 24 Hours With Chemotherapeutic Agents and rHuTNF*

Cell Line	Doxorubicin and rHuTNF, %	Dactinomycin and rHuTNF, %	Methotrexate and rHuTNF, %	Cisplatin and rHuTNF, %	Fluorouracil and rHuTNF, %
UM-SCCa 8	36.3	53.5	0.3	0	0
UM-SCCa 25	21.2	20.9	0	0	0
FaDu	23.1	29.9	0	0	0
KB-17	67.2	74.5	0	1.7	0.3
HEp-2	0.1	1.6	4.1	1.5	5.7
UM-SCCa 5	0.3	2.3	0	0	0

*rHuTNF indicates recombinant human tumor necrosis factor alpha. Percent augmentation as calculated from: $1 - (a/b) \times 100$ = percent augmentation of cytotoxicity by rHuTNF, where a = mean cell viability with drug and rHuTNF as determined by MTT assay, and b = mean cell viability with drug alone as determined by MTT assay.

served viability microscopically in culture via vital dye exclusion. Significant cytotoxicity with TNF alone was observed on one of three laryngeal carcinoma cell lines. Only a cytostatic effect was seen with three salivary gland carcinoma cell lines. This is in contrast with the current study that found no inhibitory or cytotoxic effect of rHuTNF on any of the SCCa lines investigated.

The mechanism of synergism between rHuTNF and the two antitumor antibiotics remains obscure. Postulated mechanisms for the synergistic effect of rHuTNF and doxorubicin or dactinomycin include adversely affecting DNA topoisomerase II, inhibition of RNA synthesis, and the intracellular generation of free radical molecules.[6,7,11] It is apparent from this study that some squamous cell lines are susceptible to simultaneous treatment with a combination of these agents. A significant potentiation of cytotoxicity with methotrexate, cisplatin, or fluorouracil could not be demonstrated from these experiments. The agents that were potentiated by rHuTNF in this study are not the first-line chemotherapeutic drugs for head and neck cancer, although recently Cobleigh et al[12] have shown significant response rates (44%) with doxorubicin as the sole agent in 8 of 18 previously untreated patients with SCCa of the head and neck.[13] Moreover, it has been shown by Wustrow et al[13] that in vitro squamous carcinoma cell lines showed different susceptibility to chemotherapeutic drugs as compared with therapeutic responses in patients. Clinical studies will thus be needed to evaluate in vivo the value of the rHuTNF synergism with chemotherapeutic agents for head and neck cancer.

Future clinical studies using combinations of recombinant cytokines may enhance the poor record of conventional chemotherapy in the treatment of SCCa of the head and neck. Williamson et al[14] reported that the exposure of human cancer cells to TNF and human interferons results in an effect greater than either cytokine alone. Other investigators have also demonstrated improved antineoplastic effects on tumor biopsy specimens when these cytokines were used in combination.[15] These improved effects may be the result of the induction of synthesis of TNF receptors by interferon gamma as shown by Ruggiero et al.[16] Others have noted that the combination of TNF and interferon gamma causes a reduction in c-*myc* expression in HeLa cells greater than either factor alone.[17] The expression of c-*myc* is associated with the competence of a cell for cell division. It is postulated that the loss or disruption of the control elements for c-*myc* may play a role in the activation of tumorigenesis.[17] The applicability of these findings to SCCa of head and neck origin is being investigated.

Recombinant human tumor necrosis factor (TNF-α) was provided by Knoll Pharmaceuticals, Whippany, NJ. The chemotherapeutic agents were provided by the Department of Pharmacy, University of Iowa Hospitals, via the following suppliers: dactinomycin, Merck, Sharp & Dohme, West Point, Pa; doxorubicin, Farmitalia Carlo Erba Spa, Milan, Italy; methotrexate, Lederle Parenterals Inc, Carolina, Puerto Rico; fluororouracil, Solopak Laboratories, Franklin Park, NY; and cisplatin, Bristol-Myers Oncology Products, Syracuse, NY.

Human squamous cell carcinoma lines derived from the hypopharynx (FaDu), larynx (HEp-2), and oral cavity (KB-17) were provided by the American Type Culture Collection, Rockville, Md. Cell lines from the supraglottic larynx (UM-SCCa 5) and oral cavity (UM-SCCa 8 and UM-SCCa 25) were provided by Thomas Carey, PhD, University of Michigan, Ann Arbor.

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The Analysis of Natural Killer Cell Activity by Flow Cytometry

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• A flow cytometric assay was used to detect the lytic and binding capacities of both fresh peripheral blood lymphocytes and purified Leu-19⁺ natural killer cells against head and neck cancer cell lines. Results demonstrated that natural killer cell–mediated cytotoxicity and effector-target conjugate formation evaluated by flow cytometry was significantly correlated with the standard chromium 51 release assay and the single-cell microscopic assay, respectively. The sorted Leu-19⁺ natural killer cells demonstrated higher lytic capacity with a corresponding higher binding rate compared with the unsorted peripheral blood lymphocytes and sorted Leu-19⁻ cells. Flow cytometric analysis of natural killer cell activity (a rapid, simple, and quantifiable procedure) is an alternative to the standard chromium 51 release assay.

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Two basic immunologic defense mechanisms may prevent tumor growth and progression: natural killer (NK) cells, which recognize primitive or nonself cells, and T cells, which recognize self in an altered state.[1-3] The two mechanisms serve the host in recognizing and destroying the heterogeneous population of tumor cells that express various degrees of cellular differentiation.[4,5]

There are three common and fundamental steps during cell-mediated cytotoxicity: (1) target-effector conjugate formation, (2) delivery of the lethal hit, and (3) recycling and repeating the actions (under appropriate circumstances).[6]

The most commonly used assays, ie, the chromium 51 (^{51}Cr) release and microscopic single-cell assay, which evaluate these cytotoxic phenomena, have several disadvantages in their use in clinical medicine. They are labor-intensive, are subject to laboratory-induced error, and require use of radioisotopes. To overcome these disadvantages, we report here the use of flow cytometry to estimate NK binding and cytotoxicity. The specific goals of this study were to determine the value of flow cytometry in identifying different stages of NK cell–tumor interaction and to compare these results with standard ^{51}Cr release and single-cell assays. We also investigated whether the number of NK cells and their percent of binding rate can predict their lytic potential.

PATIENTS AND METHODS

Patients

Eighteen patients were assessed for NK cell activity. Sixteen of them had not been treated previously. One patient had a recurrent tumor previously treated with radiation and one patient who had no evidence of disease had previously been treated with surgery and radiation.

Preparation of Cell Lines

Two squamous cell carcinoma (SCC) cell lines, previously established by explant outgrowth techniques,[7] were used. Line MDA183 was derived from a well-differentiated (WD) SCC of the tonsil, and line MDA1386 was derived from a lymph node of a patient with a poorly differentiated (PD) SCC of the hypopharynx. The tumors were classified according to their degree of differentiation as determined by the percentage of keratinized cells: WD indicates 75% or more, and PD indicates 25% or less. K562, an erythroleukemia cell line, was maintained in culture in RPMI supplemented with 10% fetal calf serum.

Preparation of Effector Cells

Lymphocyte-rich mononuclear cells were isolated by centrifugation at 500*g* for 50 minutes on a Ficoll-diatrizoate sodium density gradient (specific gravity, 1.1077; Bionetics, Charleston, SC). Monocytes were removed by their characteristic adherence to plastic.

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^{51}Cr Release Assay

The assay has been described in detail previously.[8] Effector cells were mixed with 10 000 ^{51}Cr-labeled target cells, either the K562 or the squamous cell cancer cell lines, in multiple ratios from 50:1 to 6:1 and centrifuged for 1 minute at 200g in flat-bottomed microtiter plates in triplicates in a total volume of 0.2 mL. Cells were subsequently incubated at 37°C in 5% carbon dioxide, for 6 hours prior to testing. One hundred microliters was removed from each well, and the radioactivity was counted for 1 minute.

Percent of cytotoxicity was computed according to the following formula:

[(Experimental Mean cpm − Spontaneous Mean cpm)/(Maximum Mean cpm − Spontaneous Mean cpm)] × 100

Maximum release was determined by incubating target cells in 10% Triton-X 100 for 6 hours at room temperature.

Expression of Lytic Units (LUs)

Data were expressed as the number of LUs per 10 million peripheral blood lymphocytes (PBLs). An LU was defined as the number of PBLs needed to effect 25% cytotoxicity of 10 000 target cells.

Immunofluorescence Labeling and Cell Sorting

The PBLs were labeled with monoclonal antibodies (MAbs) according to manufacturer's specifications for flow cytometric analysis. In each instance, 1 million PBLs or tumor cells were suspended in 50 μL of Dulbecco's phosphate-buffered saline plus 0.2% sodium azide before the respective MAb was added. Isotype-matched fluorescein isothiocyanate- and phycoerythrin-conjugated antibodies were used as controls to exclude Fc-related binding; all procedures were performed at 4°C. Typically, 10 000 cells were analyzed for single-color and two-color immunofluorescence. The MAbs used in cell-surface staining of effector cells were CD45 and anti-Leu-19 (Becton Dickinson, Mountain View, Calif). CD45 is an anti-human leukocyte antibody to the HLe-1 antigen and is expressed on all human leukocytes (clone 2D1). Anti-Leu-19 is a human lymphocyte antibody to the Leu-19 antigen expressed on essentially all NK cells (clone MY 31). For separation of Leu-19$^+$ cells, 20 million PBLs were stained and sorted with a cell sorter (FACStar Plus, Becton Dickinson, Sunnyvale, Calif). Cell viability after sorting by trypan blue exclusion exceeded 95%. The purity was at least 90%. Less than 3% contamination of Leu-19$^+$ cells existed within the negative population. Morphologically, more than 90% of Leu-19$^+$ cells were large granular lymphocytes.

Target Binding Assay and Single-Cell Agarose Assay

The method of Bonavida et al[9] was used with minor modifications. Lymphocytes and targets were first equilibrated separately at 37°C at a concentration of 2 million per milliliter. Using an effector-to-target ratio of 1:1, 150 μL of each was added to 12 × 75-mm glass tubes, which were gently centrifuged at 50g for 2 minutes and then placed in a 37°C waterbath for 20 minutes. The tubes were centrifuged at 50g for 5 minutes at room temperature, drained over gauze, and wiped with a tissue to 0.5 cm above the pellet. A 2% agarose solution was kept molten at 45°C and mixed with RPMI to a final agarose concentration of 1.33%. To prepare the slides, 50 μL of RPMI fetal calf serum was run down the side of the tube, quickly followed by 50 μL of molten agarose added directly on top, and then mixed four to five times with a micropipettor. The tube was inverted and the mixture tapped onto a precoated glass slide and spread evenly over the entire slide. After air drying for 1 to 2 minutes, the slide was stored in RPMI supplemented with 10% fetal calf serum until cells were counted. The percent of binding was calculated by dividing the number of bound effectors by the total number of effectors. At least 200 effectors were counted on each slide.

Flow Cytometry Cytotoxicity and Binding Assay

The flow cytometry assay was performed parallel with the ^{51}Cr release assay at the same effector-to-target ratios. Effector cells were mixed with 10 000 target cells in 12 × 75-mm plastic tubes, in triplicates, in a total volume of 0.2 mL. Cells were centrifuged for 1 minute at 200g and subsequently incubated at 37°C in 5% carbon dioxide, for 6 hours. Twenty minutes prior to the end of incubation, the cell pellets were resuspended in propidium iodide (20 μL/mL in phosphate-buffered saline) (Sigma Chemical Co, St Louis, Mo). After incubation, the cells were kept on ice until analysis. Samples were assayed on the cell sorter and the data were analyzed using the FACStar Research Software Package (Becton Dickinson). A minimum of 10 000 events were collected on each sample. The analysis was performed by setting the "gate window" on the target cells on the forward scatter vs side scatter dot plot screen. The markers were set to determine the dead cell background on the histogram of the target cells incubated alone, at the same concentration and volume as the test population.

The flow cytometry binding assay was performed after staining the effector cells with CD45. The lymphocyte and target preparations were treated in the same fashion as described in the single-cell agarose assay. They were equilibrated separately at 37°C at a concentration of 2 million cells per milliliter. Using a 1:1 effector-to-target ratio, 150 μL of each was added to 12 × 75-mm tubes, which were centrifuged at 50g for 2 minutes. After a 20-minute waterbath at 37°C, a minimum of 10 000 events were collected. The percent of binding was calculated by dividing the number of bound effectors by the total number of effectors.

RESULTS

Correlation Between Flow Cytometry Analysis of Cell-Mediated Cytotoxicity and ^{51}Cr Release Assay

The effector and target cells (including K562 and both SCC cell lines) could be distinguished according to their size (forward scatter) and density (side scatter) characteristics. Figure 1 shows results with K562 as an illustrative example, and demonstrates that the percentage of the gated nonviable and viable target cells can be calculated through their contour graphs or histograms. The viability of target cells incubated alone for 6 hours gives the spontaneous death or background values (Fig 1).

Figure 2 shows that the mean ± SEM cytotoxic values of the ^{51}Cr release and the flow cytometric assays were not significantly different at any ratio against K562 and MDA1386 targets. One representative experiment is shown in Fig 3. Results were similar testing the sorted Leu-19$^+$, Leu-19$^-$, and unsorted PBLs against three different targets, ie, K562, MDA1386, and MDA183 (Fig 4).

Using unsorted PBLs, as is customary for standard cytotoxicity assays, the correlation between the two assays after transformation of data to LU values against K562 ($r = .90$; $P < .001$) and MDA1386 ($r = .76$; $P < .001$) was highly significant (Fig 5). Because of minimal activity against MDA183, the correlation between the two assays with the latter cell line was not tested.

Correlation Between the Rate of Effector-Target Conjugate Formation by Flow Cytometry and the Single Cell Assay

After staining the effector cells with CD45 and performing the target cell

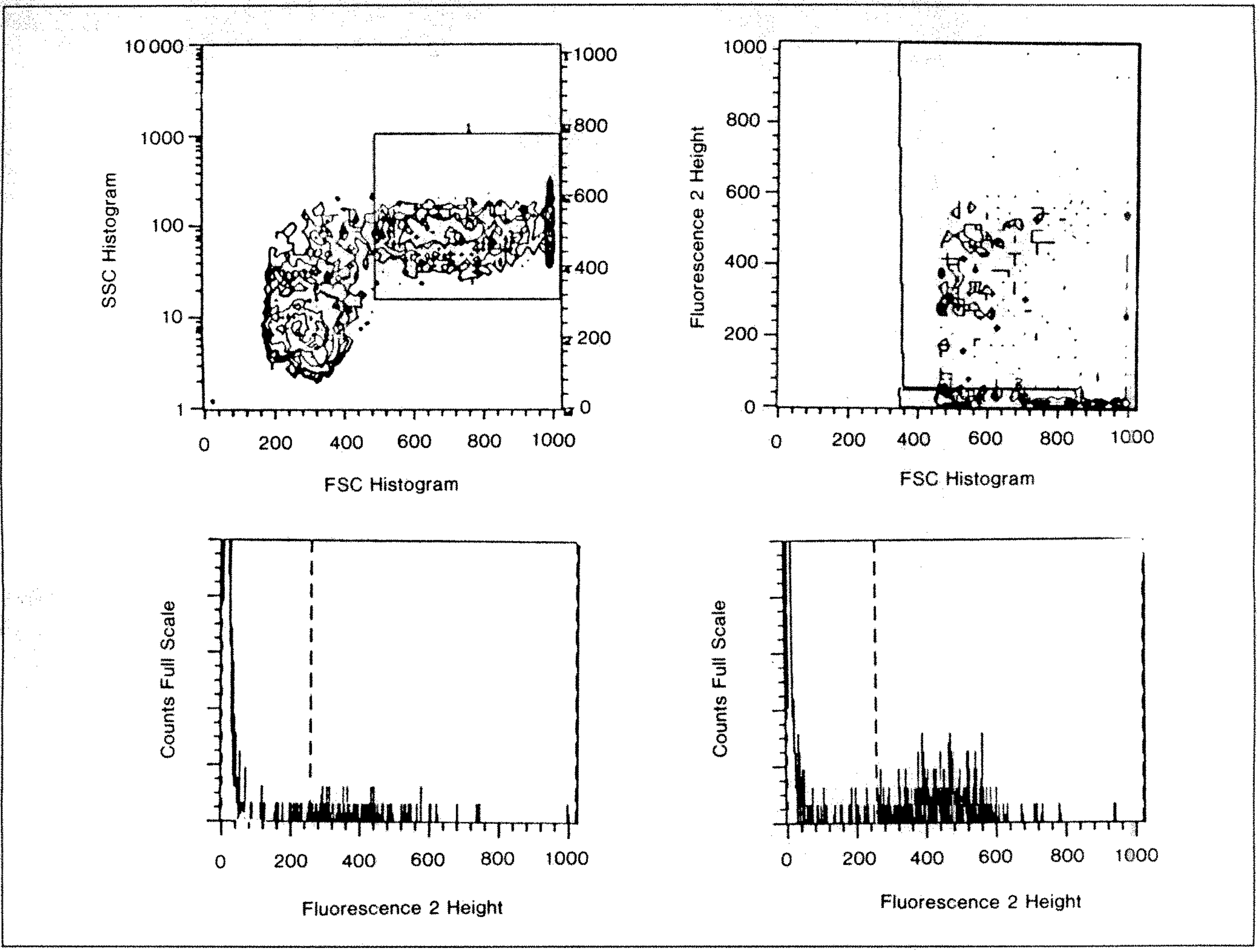


Fig 1.—Analysis of the natural killer cell-mediated cytotoxicity by flow cytometry. Top left, the gate is set on the K562 target cells on the forward scatter (FSC) vs side scatter (SSC) dot plot distribution of the mixed lymphocyte/tumor cell populations. Furthermore, the same gate is used during the analysis. Bottom left demonstrates the dead cell background determination (5% of the total population) for control target cells (ie, target cells incubated alone for 6 hours) by histogram due to their fluorescence intensity by propidium iodide uptake. Using the same marker position for the effector-target mixture, the determination of the viable vs nonviable target cell after 6-hour incubation at an effector:target ratio of 50:1 are represented in histogram (bottom right) and in dot plot distribution (38% cytotoxicity) (top right).

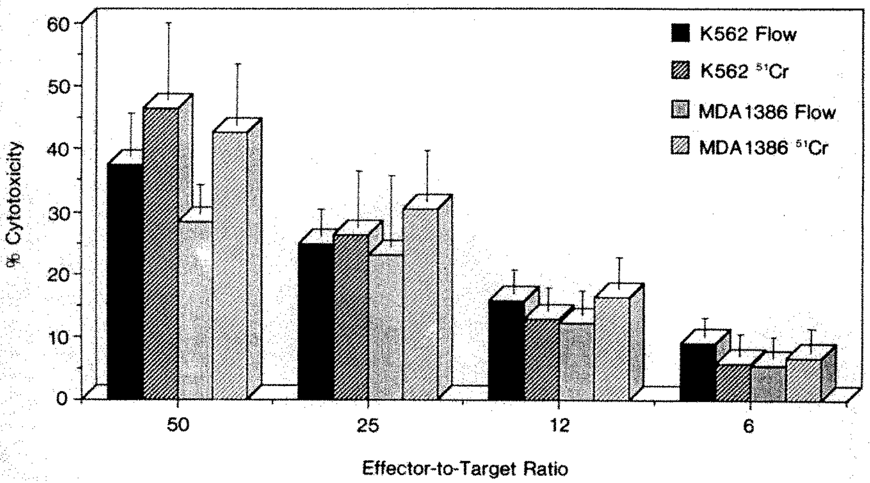


Fig 2.—The mean cytotoxicity values at different ratios determined by flow cytometry and ^{51}Cr release assays. Results represent 12 experiments against K562 and 9 experiments against MDA1386 target cells. Lines over bars indicate SEM.

binding, we easily distinguished three populations (effector cells, target cells, and conjugates) according to size and fluorescence intensity (Fig 6). After the sorting window on the conjugate population was set and the population was sorted, a microscopic analysis confirmed a high proportion of conjugate formation contained within window 1, as we expected (Fig 6). The results of the single-cell and flow cytometric assays for binding capacity were nearly identical (Table 1). Thus, values from the assays can be used interchangeably.

Finally, we compared the rate of target cell binding as determined by flow cytometry, as well as the percentage of Leu-19$^+$ positive PBLs, with the

LU values against both K562 and MDA1386 target cells (Table 2). Should either the percentage of binding or the percentage of Leu-19$^+$ directly relate to the LU value, then all assessments could potentially be used interchangeably. This would greatly simplify determination of natural immune status. The cumbersome cytotoxicity assays could be eliminated. Results of the comparison showed that only the relationship between percentage binding and LU activity against MDA1386 was significant ($r = .82$; $P < .01$). No other significant relationships were noted. Table 3 reveals further that it is the Leu-19$^+$ population that binds and kills most readily the respective target cell population. No significant lysis was mediated by the Leu-19$^-$ population.

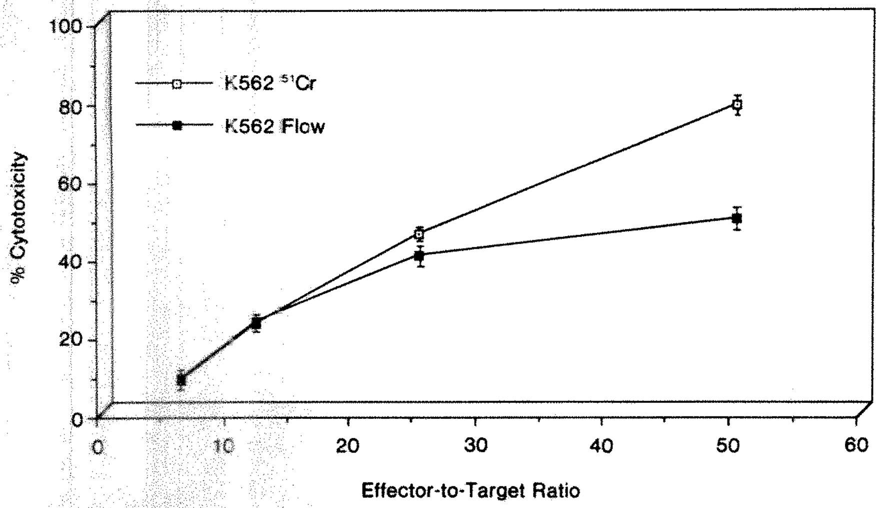
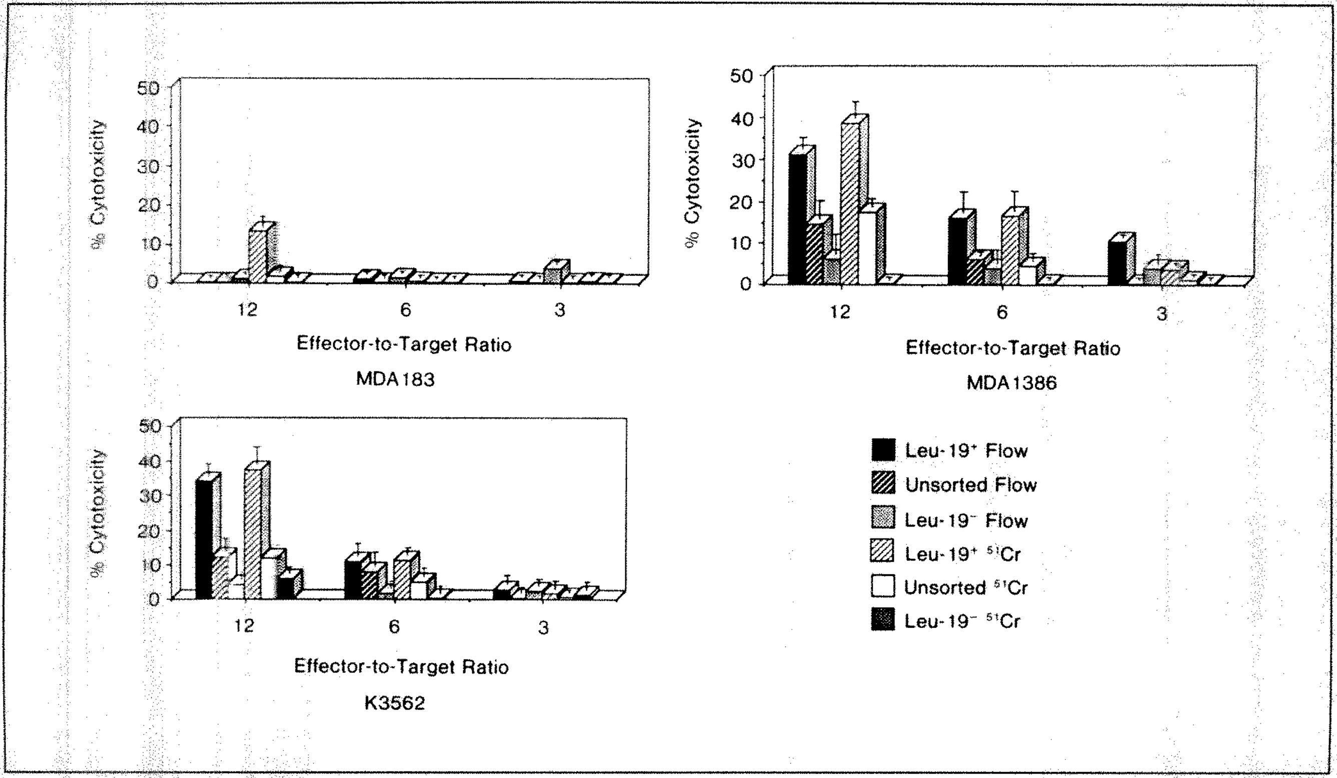


Fig 3.—One representative experiment of the comparison between flow cytometry and ^{51}Cr release assay. Each experiment was performed in triplicate wells. Vertical bars represent SEM.

Fig 4.—Cytotoxicity values of the Leu-19$^+$ effector cells, unsorted PBLs, and Leu-19$^-$ effector cells against K562, MDA1386, and MDA183 target cells. Means of three distinct experiments. Lines over bars indicate SEM.



COMMENT

These results offer alternative methods, compared with traditional NK cell functional assays, for both a better understanding of the factors that contribute to NK cell-mediated lysis and an improved means of applying this clinically relevant information to day-to-day assessment of patients with head and neck cancer.

The most commonly used method for detecting only the end results of these processes is the ^{51}Cr release assay. Some of the disadvantages of this assay are the use of radioactive material and the difficulty of reproducing data from laboratory to laboratory. Some target cells are refractory to labeling and others (especially fresh tumor cells) may spontaneously release large

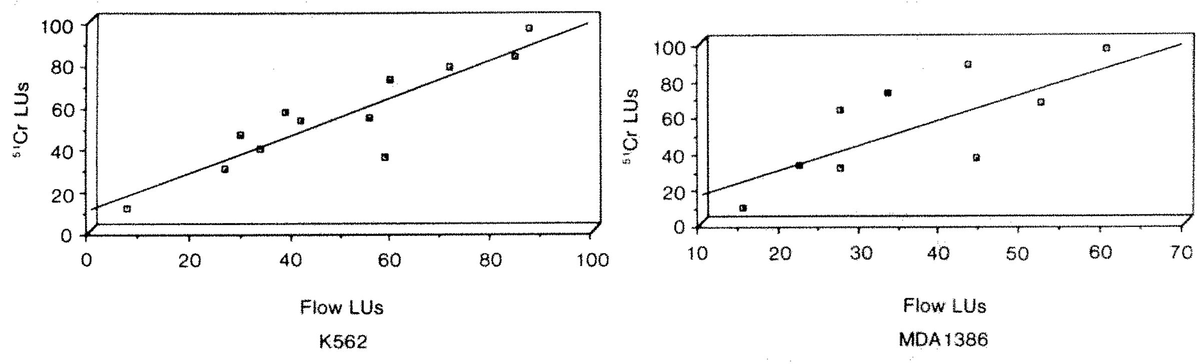


Fig 5.—The correlation between the flow cytometry and ^{51}Cr release lytic unit (LU) values with K562 (left) and MDA1386 (right).

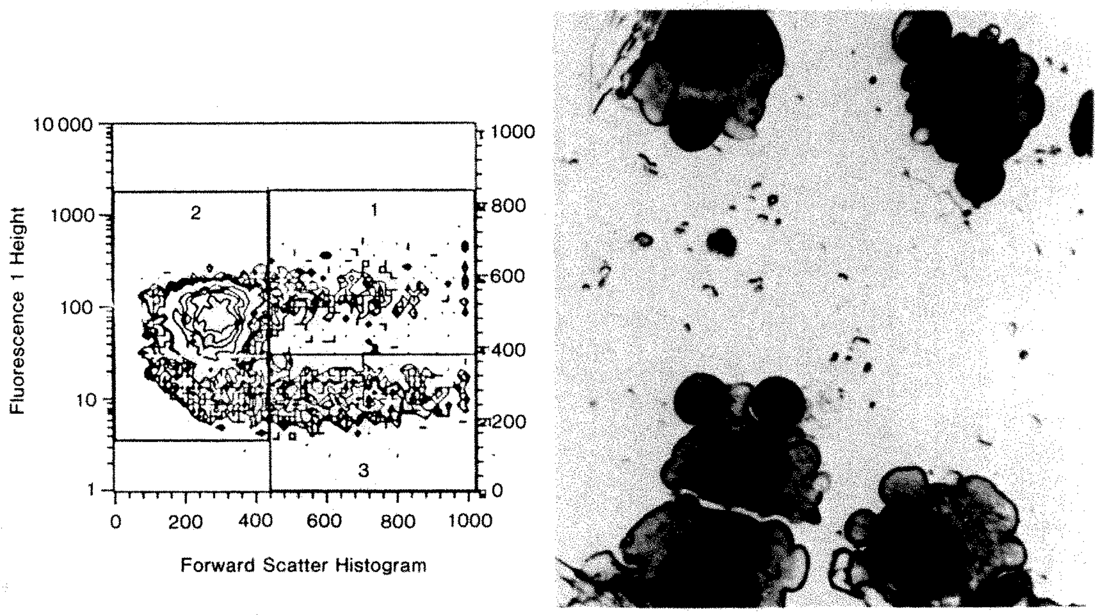


Fig 6.—Left, Dot plot distribution of MDA1386 target cells (window 3), the peripheral blood lymphocytes stained by CD45 monoclonal antibody (window 2), and the conjugates (window 1) formed between peripheral blood lymphocytes and the target cell. Right, Cells in window 1 were sorted and stained with May-Grünwald;the slide shows the conjugate formation.

amounts of ^{51}Cr.[10] Another standard assay used for understanding the process of binding and recycling of killer cells against cancer targets, namely, the direct microscopic single-cell assay, has been developed. This assay provides information on a single-cell level about effector-target cell conjugate formation and lysis. The assay is laborious and difficult to quantitate because fewer cells are counted.

Past studies have evaluated flow cytometry as a method to evaluate cell-mediated cytotoxicity by examining the release of various fluorescein dyes from the lysed target.[10-12] Although flow cytometric assays in these studies provided cytotoxicity results that were comparable with the ^{51}Cr release assay, there was a time limit because of a relatively rapid leakage of the dye with a concomitant high spontaneous release from the target cell. Thus, the period of incubation of the combined effector-target populations in order to generate lysis was limited. In addition, calculation of the results is complicated, limiting this method's day-to-day practicality.

Recently, propidium iodide dye exclusion was used to determine the number of dead cells.[13] Propidium iodide dissolves in an isotonic solution, and its entry into living cells is prevented by the intact cell membrane. Hence, fluorescence is seen only in the nuclei of dead cells. The technique, as has been demonstrated in our study, makes possible the measurement of both live effector and target cells within the same sample and allows the effector-to-target ratio to be more accurately estimated. In our assay, the success of the method was based on the observation that the target cells in question were distinguishable from the effector cells based on their volume characteristics. However, as perhaps in circumstances of interleukin 2 stimulation of lymphocytes when all populations are identical in size, target cells can be identified by staining the target with a fluorescent dye, CFDA[11] or PKH-I.[14]

The detection of binding capacity was made possible in our study by labeling the effector cells with fluorescein isothiocyanate-conjugated CD45 surface marker, which is a pan-antileukocyte antibody. In our study, CD45 did not inhibit lysis (data not shown). Other investigators also have not found any effect on NK cell function.[15] Because conjugate formation largely depends on centrifugation,[16] and the percentage of conjugate increases as high speed increases, we strictly maintained the same conditions used for the microscopic single-cell assay. Interestingly, results from this initial study showed that NK cell activity could be predicted simply through the quantitation of percentage of PBLs binding a specific target; specifically, in this instance, the MDA1386. The establishment of a reliable prediction model for NK cell function would make the cytotoxicity assay unnecessary and would provide a simple method for determining the lytic potential of the effector population on a daily basis. In that regard, only the measure of PBL binding with MDA1386 significantly correlated

Table 1.—Comparison of the Binding Results of the Flow Cytometric Technique vs Microscopic Single-Cell Assay*

	Effector Cells, % Binding					
	Leu-19⁺		Unsorted PBLs		Leu-19⁻	
Targets	Microscope	Flow	Microscope	Flow	Microscope	Flow
K562	23 ± 4	26 ± 6	16 ± 5	20 ± 6	10 ± 3	16 ± 6
MDA1386	23 ± 3	23 ± 4	17 ± 3	18 ± 4	11 ± 2	15 ± 4
MDA183	13 ± 2	15 ± 2	11 ± 2	11 ± 1	7 ± 2	7 ± 2

*Data are the means ± SEMs of three distinct experiments of effector (Leu-19⁺, unsorted peripheral blood lymphocytes [PBLs] and Leu-19⁻) and target (K562, MDA1386, and MD183) conjugates.

Table 2.—Correlation of the Peripheral Blood Lymphocyte Binding Capacity and Percent of Leu-19⁺ Cells Within the Peripheral Blood With Lytic Units (LUs) Against K562 and MDA1386

	K562			MDA1386		
Experiment No.	% Leu-19⁺*	% Binding†	LUs, No.	% Leu-19⁺*	% Binding†	LUs, No.
1	9	20	1	16	5	8
2	10	6	10	11	19	30
3	9	36	26	13	17	31
4	21	34	34	9	24	35
5	11	19	38	26	21	62
6	27	19	45	22	20	66
7	26	28	52	13	28	71
8	22	26	53	21	24	87
9	13	23	56	25	41	95
10	13	28	59	...	...	...
11	13	24	65	...	...	...
12	16	29	71	...	...	...
13	25	42	77	...	...	...
14	15	19	111	...	...	...
15	14	34	128	...	...	...
16	25	33	278	...	...	...

*Percentage of Leu-19⁺ cells within peripheral blood lymphocytes.

†Percentage of peripheral blood lymphocytes that bind to the respective target as determined by flow cytometry.

Table 3.—Comparison of the Leu-19⁺, Unsorted Peripheral Blood Lymphocyte (PBL), and Leu-19⁻ Cell Binding With Lytic Capacity Against K562, MDA1386, and MDA183 Target Cells

		K562			MDA1386			MDA183		
			LUs, No.			LUs, No.			LUs, No.	
Experiment No.	Effectors	% Binding*	^{51}Cr	Flow	% Binding*	^{51}Cr	Flow	% Binding*	^{51}Cr	Flow
1	Leu-19⁺	38	133	117	36	122	133	22	28	0
1	Unsorted PBLs	28	52	41	21	62	27	17	0	0
1	Leu-19⁻	10	0	0	8	0	9	7	0	0
2	Leu-19⁺	34	125	111	35	142	111	22	37	0
2	Unsorted PBLs	26	38	55	20	66	52	17	9	0
2	Leu-19⁻	10	8	0	7	0	6	6	0	0
3	Leu-19⁺	30	91	105	35	111	95	23	41	0
3	Unsorted PBLs	23	27	20	26	60	0	18	0	0
3	Leu-19⁻	8	0	0	9	0	0	7	0	0

*Percentage of PBLs that bind to respective target by flow cytometry.

with NK cell function against the same cell line in this preliminary study. No predictive measure was identified by simply quantifying the percentage of Leu-19$^+$ lymphocytes, and neither measure was predictive of NK activity against K562.

Given that the quantitation of NK cell function has prognostic implication for risk of metastases from PD head and neck cancers, the relationship of binding to the cell line MDA1386 by PBLs to cytotoxic function against that cell line may have clinical relevance.[17] Binding as measured by flow cytometry to this PD head and neck cancer cell line may thus in itself provide prognostic information. This can be performed on a routine basis and should be easy to standardize between laboratories.

The insufficient cytotoxic and binding ability of the NK cell against cell lines derived from a WD head and neck cancer vs a cell line derived from a PD head and neck cancer extends our previous observation regarding the importance of the recognition, binding, and lytic capacity of the NK cells against dedifferentiated cancer.[17-20]

Previous studies have shown the prognostic information of NK cell function within patients with head and neck cancer.[17-20] In regard to the development of regional and distant metastasis, patients with PD SCCs and low NK function had the most prognostic information, while no relationship between NK function and risk of metastatic disease could be identified in those individuals with WD lesions.[17] These in vivo observations were extended by the in vitro data, demonstrating that PD head and neck cancer target cells are highly sensitive to changes in lytic function expressed by non-major histocompatibility complex effector cells.[20] Future work based on the present study may provide more information in the cellular level of this phenomenon. Such information not only will allow us to understand better the biology of head and neck cancer, but also may indicate the appropriate clinical use of biologic response modifiers.

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Carotid Body Paragangliomas

A Clinicopathologic and DNA Analysis of 13 Tumors

Leon Barnes, MD, Suzanne R. Taylor, MD, PhD

• The clinical and pathological features of 13 carotid body paragangliomas from 12 patients were examined and correlated with the DNA ploidy pattern as determined by image analysis. These tumors occurred in 7 women and 5 men aged 19 to 62 years (average, 42 years). All presented with a slowly enlarging, usually asymptomatic mass of 2 weeks' to 25 years' duration. Two patients were related and had a family history of paragangliomas. The tumors ranged from 2 to 6 cm. All contained scattered chief cells with pleomorphic nuclei, two exhibited mitoses, and three showed perineural and three vascular invasion. Follow-up was available in all 12 patients and ranged from 15 months to 28 years (average, 7.3 years). None of the tumors recurred locally, but one did metastasize to a single cervical lymph node that was apparent at the time of diagnosis. Of 13 carotid body paragangliomas examined for DNA, 4 were diploid, 3 diploid-tetraploid, 3 tetraploid, 2 aneuploid, and 1 polyploid. The only malignant tumor was polyploid. From these observations, we conclude that abnormalities in DNA content of carotid body paragangliomas are common and that tumor ploidy cannot be used to assess malignant potential. We also found no apparent relationship among nuclear pleomorphism, mitotic activity, perineural invasion, or vascular invasion and clinical behavior. Perineural and vascular invasion, however, were observed only in tumors with abnormal DNA histograms.

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The carotid bodies are paired, bilateral, usually symmetrical aggregates of specialized neuroectodermal tissue that belong to the extra-adrenal paraganglion system.[1] They are characteristically located at the bifurcation of the common carotid artery along its posteromedial wall, either within or immediately external to the adventitia, and anchored to the artery by a band of fibrovascular tissue, the ligament of Mayer. Each measures about 3 to 7 mm in greatest dimension[1-3] and weighs 3 to 15 mg.[4]

The carotid bodies function as chemoreceptors sensitive to changes in arterial oxygen tension, carbon dioxide content, and hydrogen ion concentration, and contribute to homeostasis through regulation of the cardiopulmonary system. They are accordingly highly vascular structures, with a perfusion rate greater than that of either the heart or the brain.

Histologically, they are composed of two types of cells, chief and sustentacular, arranged in a characteristic compact alveolar or Zellballen pattern surrounded by reticulin fibers. The chief cells (type I cells, epithelioid cells) are more numerous. They have an epithelioid appearance and, ultrastructurally, contain catecholamine-bound neurosecretory granules.[5,6] The sustentacular cells (type II cells, supporting cells) in contrast are spindled, usually located near the periphery of the Zellballen, and are devoid of neurosecretory granules.

Disorders affecting the carotid bodies are infrequent and basically limited to two conditions: *hyperplasia*, seen in individuals who suffer from chronic hypoxic diseases or live at high altitudes, and *neoplasia*.[2,7] Tumors of the carotid bodies, termed *paragangliomas*, are relatively uncommon. In 1971,[8] there were about 500 cases recorded in the literature and, by 1980,[9]

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Clinicopathologic Features of Carotid Body Paragangliomas*

Case/Age, y/Sex	Side	Size, cm	Duration	Perineural Invasion	Vascular Invasion	Metastasis	Ploidy	Follow-up
1/26/F	R	6	19 y	No	No	No	Dip-Tetra	R CBPG, NED at 28 y; 9 y later developed L CBPG, NED at 19 y
2/60/F	R	2.5	2 y	No	No	No	Diploid	NED at 4 y
3/35/F	R	2.2	2 y	Yes	No	No	Aneuploid	NED at 7 y 7 mo
4/51/M	R	3	25 y	No	No	No	Diploid	NED at 1 y 7 mo
5/56/F	R	3	3 mo	No	Yes	No	Aneuploid	DOC at 2 y with NED
6/43/M	L	2.5	2 wk	No	No	No	Dip-Tetra	NED at 2 y
7/62/F	R	4.5	4 y	No	No	No	Diploid	NED at 5 y
8/37/M†	R	4	6 mo	No	No	No	Tetraploid	NED at 10 y
	L	2.3	6 mo	No	No	No	Dip-Tetra	NED at 9 y
9/19/F	L	6	2 mo	Yes	Yes	Yes (1 lymph node)	Polyploid	NED at 1 y 3 mo; also found to have simultaneous R CBPG that has not yet been removed
10/28/F	L	3	1 y	No	No	No	Diploid	NED at 13 y
11/33/M	R	4	6 mo	No	Yes	No	Tetraploid	NED at 6 y; developed R jugulotympanic paraganglioma 2 y after removal of R CBPG
12/49/M	L	6	. . .	Yes	No	No	Tetraploid	NED at 5 y 7 mo

*F indicates female; M, male; R, right, L, left; Dip-Tetra, diploid-tetraploid; CBPG, carotid body paraganglioma; NED, no evidence of disease; and DOC, died of other cause.

†The patient had simultaneous bilateral CBPGs that were excised and examined at our medical center.

the number had grown to over 900.

The typical presentation of a carotid body paraganglioma (CBPG) is that of a slowly enlarging, asymptomatic mass deep to the anterior border of the sternocleidomastoid muscle just below the angle of the mandible in a middle-aged adult. Occasionally they are associated with pain, hoarseness, dysphagia, Horner's syndrome, headache, syncope, bruit, or thrill. Some are familial or bilateral and a few occur in conjunction with paragangliomas in other sites.[9] Functional tumors with catecholamine-induced hypertension, however, are exceptional.[10]

While the majority of CBPGs are benign, 2% to 13% pursue a malignant course, with metastases directed primarily to regional lymph nodes, lungs, and bones.[7-9,11-16] Unfortunately, the clinical behavior cannot be predicted on the basis of routine histologic sections. Such features as nuclear pleomorphism, mitotic activity, necrosis of Zellballen, and vascular invasion, advocated by some as potential indicators of aggression,[17] are not absolute and have been observed in benign tumors as well.[1,14,16,18,19]

Recent studies employing immunohistochemical procedures, however, offer some hope of prognostication. Initial results indicate that tumors that contain sparse to absent sustentacular cells and express few, if any, antigens are more likely to prove aggressive.[20-23]

There are also numerous studies in the recent literature proclaiming DNA ploidy, as determined by flow cytometry or image analysis, to be a valuable adjunct in the clinical and pathologic assessment of a variety of tumors.[24-30] None of these, however, have dealt with CBPGs, as far as we are aware. Our study, using image analysis, was therefore undertaken to determine first if abnormalities in DNA content exist in CBPGs and, if so, their specific types and frequency of expression and second, whether the ploidy pattern could be used by the surgical pathologist to distinguish benign from malignant tumors.

MATERIALS AND METHODS

The pathology files of the Presbyterian-University Hospital, Pittsburgh, Pa, and the Eye and Ear Hospital of Pittsburgh (Pa) were reviewed for all cases of CBPGs accessioned over the 28-year period from 1960 through 1987. Twenty-three tumors from 22 patients were identified and confirmed histologically to be paragangliomas. Three patients had bilateral tumors, but only one of the three had both tumors removed at our medical center. Ten patients were subsequently excluded: 5 for lack of follow-up or loss of medical records and 5 because on review of the medical records, angiograms, or operative summaries, the tumors actually arose from the vagus nerve rather than the carotid body. Thirteen tumors from 12 patients (including the 1 with bilateral CBPGs) were finally selected for this study.

The clinical records of each patient were reviewed for the following information: age at diagnosis, sex, race, initial symptoms, duration of symptoms, evidence of a functioning tumor, signs or symptoms of paragangliomas in other sites or a family history of such tumors, and initial treatment. Follow-up was achieved through medical records, attending physicians, tumor registries, or telephone or written communication with the patient.

Tissue for routine light microscopy was fixed in 4% buffered formaldehyde solution and embedded in paraffin. The number of paraffin blocks containing tumor ranged from one to seven per case (median, four). In each instance, the pathology reports and existing hematoxylin-eosin–stained slides were reviewed and the following data tabulated: tumor size; number of mitoses per 10 high-power fields (high-power field, ×400); normal vs abnormal mitoses; and the presence or absence of nuclear pleomorphism, necrosis, spindle cells, fibrosis, vascular invasion, perineural invasion, or regional lymph node or distant metastases. Nuclear pleomorphism was judged as absent, occasional, or numerous, while fibrosis was semiquantitated on a scale of 0 (absent) to 4+ (marked). Based on the character of the tumor margin and presence or absence of metastases, tumors were assigned to one of three categories: noninvasive (circumscribed or pushing margins), locally invasive (poorly defined or infiltrating margins), and malignant (metastatic). Tumors were regarded as malignant only if they were associated with documented metastasis; locally invasive neoplasms did not qualify.

In four cases (cases 4, 5, 8, and 12), fresh tissue had been fixed in glutaraldehyde solution and processed for electron microscopy. The electron photomicrographs and ultrastructural reports were also examined.

For quantitative analysis of DNA, nuclei were isolated from 60-μm paraffin sections using the rehydration and pepsin digestion procedure of Hedley et al.[11] Two sections were used from a representative block for each tumor. Direct smears were prepared from the nuclear preparation and postfixed in 4% buffered formaldehyde solution. Nuclear DNA content was determined by image analysis using the Cell Analysis Systems (Lombard, Ill), integrated system of slides, hardware, and software.[12] The smears were prepared on Cell Analysis Systems on slides containing predeposited control cells and were hydrolyzed in 5N hydrochloric acid prior to Feulgen staining using the Cell Analysis Systems purified reagents. Each slide was independently calibrated using the predeposited control cells, and a minimum of 250 cells were analyzed on each side. In the majority of cases, 300 cells were analyzed. The DNA index of each population in the histogram and the number of cells in each cell cycle compartment were determined using the Cell Analysis Systems quantitative DNA analysis software module.[12,13] The histograms were classified into five types depending on the DNA index of the major population(s) and distribution of the cells. Those histograms with the major G_0/G_1 populations with a DNA index indistinguishable from 1 (0.9 to 1.15) were considered DNA diploid. Tumors with G_0/G_1 populations with a DNA index of 1 that also displayed a large (>10.0%) G_2M population at a DNA index of 2 (1.9 to 2.2) were considered diploid/tetraploid. These lesions often had a significant number of cells with DNA indexes greater than 2 suggesting the presence of a second S-phase and superimposition of the G_2M population of the diploid cells with a tetraploid G_0/G_1. Those lesions with a single G_0/G_1 population with a DNA index of 2 (1.9 to 2.2) were considered tetraploid and those tumors with a single G_0/G_1 population not equal to one or two were considered DNA aneuploid. In one of the tumors, there were three cellular populations occurring at DNA indexes of 1, 2, and 4, and this tumor was considered polyploid.

RESULTS

Clinical Findings

At the time of diagnosis, the 7 women and 5 men ranged in age from 19 to 62 years (average, 42 years; Table). Eleven were white and 1 was black. Seven patients had tumors arising from the right carotid body and 4 from the left carotid body; 1 patient had bilateral synchronous tumors.

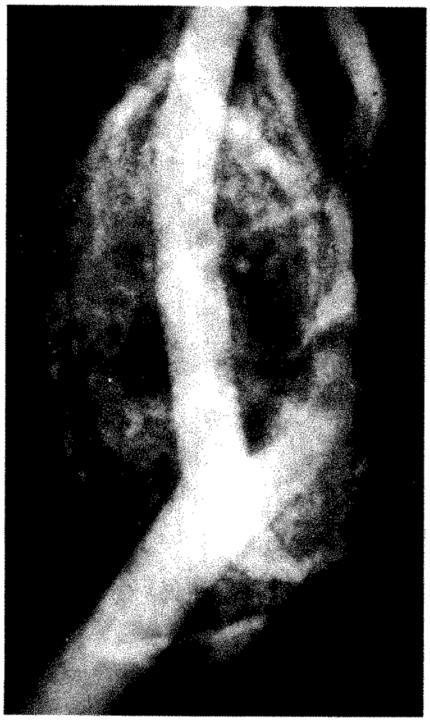

Fig 1.—Preoperative carotid angiogram showing characteristic hypervascular mass arising at the bifurcation of the common carotid artery (case 9).

All patients presented with a slowly enlarging, usually asymptomatic mass of 2 weeks' to 25 years' duration (average, 59.4 months; median, 12 months). Three experienced pain or tenderness, especially on manipulation of the tumor, and 1 also complained of hoarseness and dysphagia. Two patients were found to have hypertension which, on further evaluation, was believed to be essential. Although only 2 patients had their urine samples examined for catecholamines, no patient was believed to have a functional tumor based on signs and symptoms recorded in their medical records or operative summaries.

Multiple Paragangliomas

Four patients had multiple paragangliomas. One patient (case 1) had bilateral, asynchronous, nonfamilial CBPGs separated by an interval of 9 years. Two patients (cases 8 and 9) were related, father and daughter, and had a strong family history of such tumors. The father had three synchronous paragangliomas, bilateral CBPGs, and a right vagal paraganglioma, discovered on initial hospitalization. His daughter (case 9) also had bilateral CBPGs. In addition, the father has a sister who had a jugulotympanic paraganglioma excised and his father, in turn, has a neck mass, presumably a CBPG. The fourth patient (case 11) had two asynchronous, nonfamilial paragangliomas excised, a right CBPG, and a right jugulotympanic paraganglioma, the latter discovered 2 years after the carotid tumor.

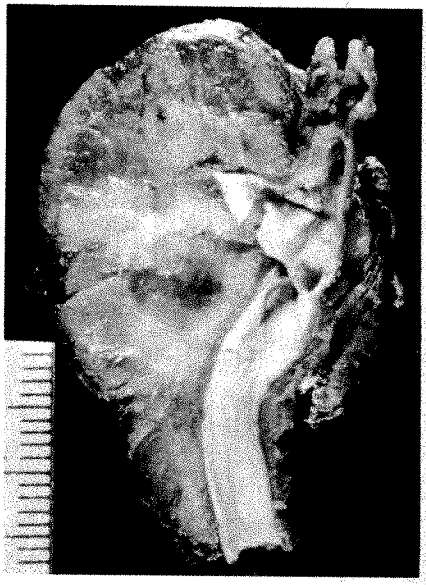

Fig 2.—Malignant carotid body paraganglioma in which segments of the common, internal, and external carotid arteries had to be sacrificed (case 9).

In case 1, the second CBPG was removed elsewhere and was not available for this study. In case 9, only one of the two CBPGs has thus far been removed; the other, verified by angiogram, is to be removed at a later date. Thus, only one of the three patients with bilateral CBPGs (case 8) had both tumors removed at our medical center and could be compared in this study.

Treatment and Follow-up

Preoperative carotid angiograms were obtained on all patients. Each demonstrated a characteristic, highly vascularized mass at the bifurcation of the common carotid artery (Fig 1).

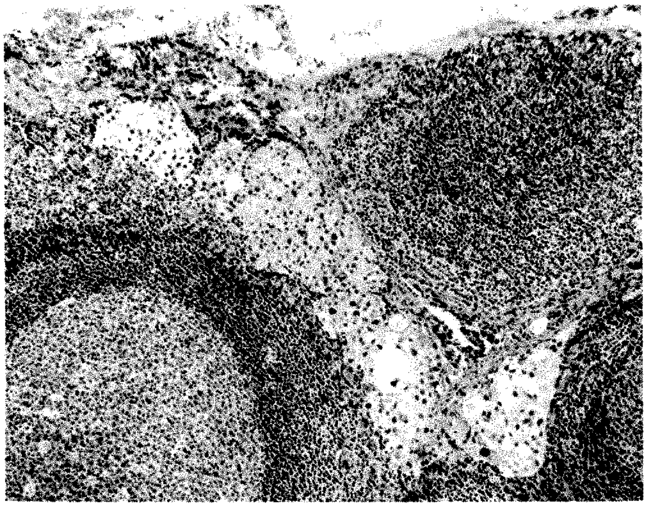

Fig 3.—Unsuspected lymph node metastasis in case 9 (hematoxylin-eosin, ×125).

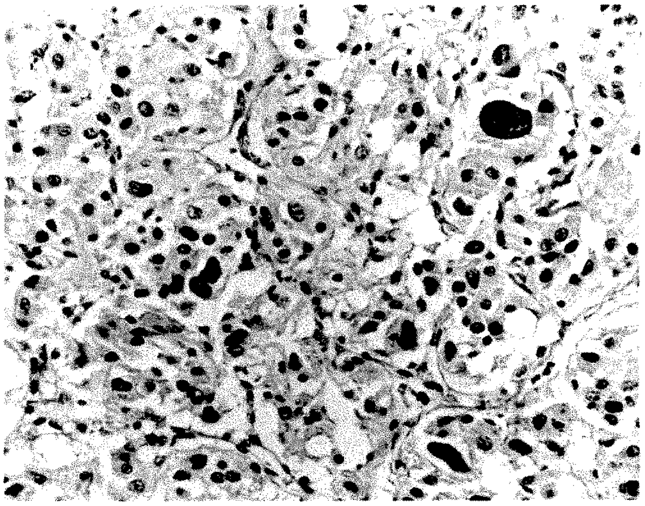

Fig 4.—Typical Zellballen arrangement of chief cells. Note the enlarged, hyperchromatic nuclei (hematoxylin-eosin, ×125).

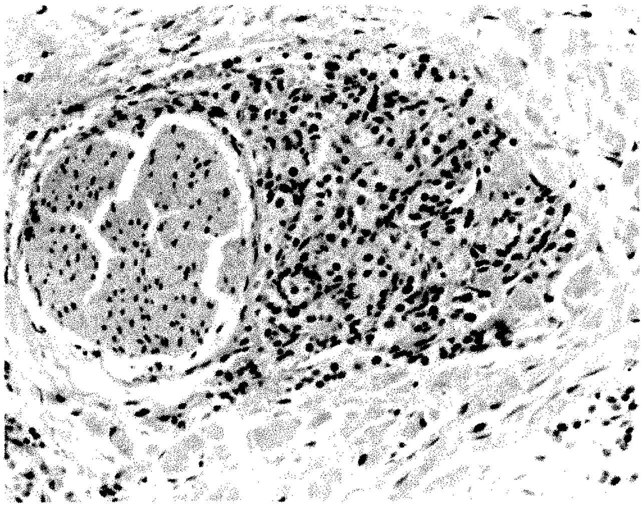

Fig 5.—Perineural invasion (case 9) (hematoxylin-eosin, ×250).

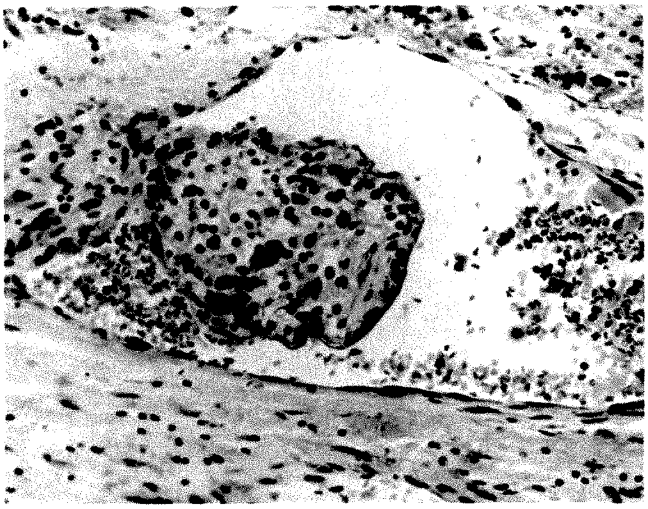

Fig 6.—Vascular invasion (case 9) (hematoxylin-eosin, ×315).

All patients were treated by surgery and, of these, only 1 underwent preoperative gelatin sponge (Gelfoam) embolization to reduce the blood supply of the tumor. The great vessels of the neck were preserved in 8 cases; however, in 3 cases, a segment of the external carotid artery had to be sacrificed and, in another case, portions of the common, internal, and external carotid arteries were removed (Fig 2).

Lymph nodes, either purposely or inadvertently, were removed during excision of 12 of 13 CBPGs. The number of nodes removed varied from one to 12 per tumor. All of these were benign with the exception of case 9. In this instance, a single excised lymph node (0.5 cm) contained metastatic paraganglioma (Fig 3). The patient subsequently underwent a left radical neck dissection and all 37 additional lymph nodes were free of tumor.

Follow-up was available in all 12 patients and ranged from 15 months to 28 years (average, 7.3 years; median, 5.6 years). No patient thus far has developed local recurrences and, with the exception of case 9, none has developed regional or distant metastases. The single patient with a malignant CBPG metastatic to a cervical lymph node is currently free of disease 15 months after her operation.

Four patients either had, or subsequently developed, additional paragangliomas. See the "Multiple Paragangliomas" section.

Pathological Findings

The tumors ranged from 2 to 6 cm in greatest dimension (average, 3.8 cm) and were firm, rubbery, well circumscribed, and invested by a thin, sometimes focally thickened, fibrous capsule. On cut surface, most had a variegated yellow, tan, pink, red, or brown appearance with areas of fibrosis and hemorrhage (Fig 2). A few, however, were uniformly tan-pink or yellow-brown. A large artery, usually the external carotid, was occasionally seen coursing through the tumor or attached peripherally.

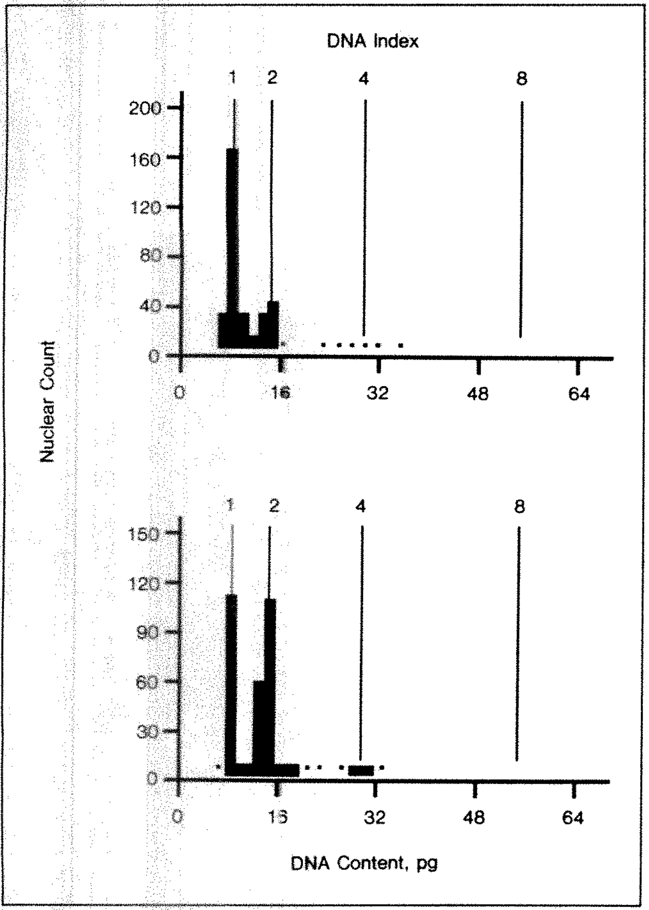

Fig 7.—DNA histograms illustrating diploid-tetraploid and polyploid patterns. Top, Left carotid body paraganglioma removed from case 8. The major G_0/G_1 population occurs at a DNA index of 1.04 and the second peak occurs at a DNA index of 2.04. The second peak contains 20% of cells. The cells above a DNA index of 2 suggest a second S phase. Bottom, Histogram from case 9. There are populations occurring at DNA indexes of 1.00, 1.99, and 4.02.

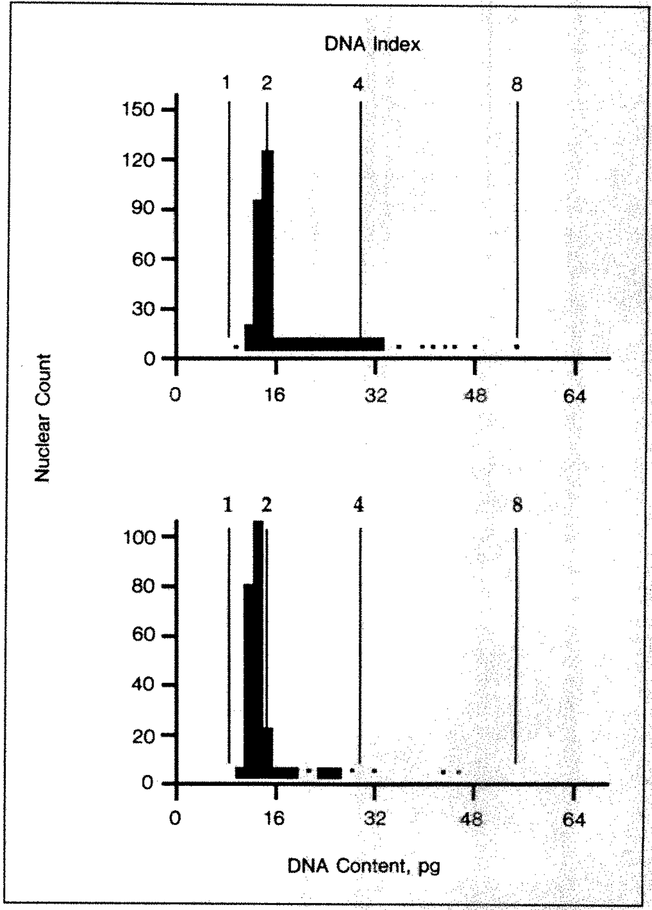

Fig 8.—Representative DNA tetraploid and aneuploid histograms. Top, The G_0/G_1 peak occurs at a DNA index of 2.02 (case 12). Bottom, The G_0/G_1 peak occurs at a DNA index of 1.74 (case 3).

Microscopically, all tumors exhibited the typical Zellballen or alveolar arrangement of chief cells with admixed, inconspicuous sustentacular cells separated by a prominent capillary network (Fig 4). The alveolar clusters, for the most part, contained 20 to 50 cells but some had as few as three or four to as many as 75 or more cells. The chief cells generally had an epithelioid appearance with mild to moderate amounts of light to dark pink, sometimes clear cytoplasm, and uniform, vesicular nuclei. In rare instances, the cells had basophilic, finely granular cytoplasm and, in one tumor, they focally assumed a spindled configuration. Chief cells with one or more enlarged, pleomorphic, hyperchromatic nuclei, often with prominent nucleoli and intranuclear inclusions of cytoplasm, were observed in all cases (Fig 4). These cells were occasional in seven tumors and numerous in six tumors.

Two tumors had mitoses. In case 7, only one mitosis per 10 high-power fields was seen, while in case 9 (the only malignant CBPG), there were two mitoses per 10 high-power fields, one of which was abnormal. Three tumors demonstrated perineural invasion (cases 3, 9, and 12) and three demonstrated vascular invasion (cases 5, 9, and 11) (Figs 5 and 6). Fibrosis, sometimes with hemosiderin deposits, was absent in 2 lesions, 1+ in 1, 2+ in 4, 3+ in 4, and 4+ in 2. All 13 tumors had noninvasive or circumscribed margins and none exhibited necrosis. A few also contained small, random collections of lymphocytes.

Tumor Ploidy

Of 13 CBPGs examined, 31% were diploid, 23% diploid-tetraploid, 23% tetraploid, 15% aneuploid, and 8% polyploid (Figs 7 and 8). Evidence of tumor heterogeneity or tumor progression was found in at least one instance. In case 1, the patient initially had a biopsy of her right CBPG before it was completely excised 15 months later. The biopsy was diploid-tetraploid, while the excised tumor was tetraploid.

In patient 8 (the patient with three synchronous paragangliomas), the right and left carotid tumors were tetraploid and diploid-tetraploid, respectively, while the right vagal paraganglioma was diploid-tetraploid (Fig 7, top). His daughter (case 9), who also was the only patient with a malignant CBPG, had a polyploid tumor (Fig 7, bottom).

COMMENT

Carotid body paragangliomas have been described in all age groups, but are uncommon in children.[7,11-14] They occur most frequently in adults averaging 45 to 50 years of age. Some reports indicate a female predominance,[11,15] others indicate a male predominance.[7,14] In a collective review of 257 cases, we found 52% males and 48% females.[7,11-15] Two percent to 13% of the tumors are malignant[7-9,11-16] and approximately 10% are familial, the latter expressed as an autosomal dominant trait.[9]

Although our study is relatively small, the findings are similar to those above. The average age of our patients was 42 years, 58% were females, 8% of the tumors were malignant, and 17% had a familial association. We, therefore, believe our series to be an adequate representation of CBPGs and its variants.

Our investigation indicates that abnormalities in DNA content of CBPGs are not only common but are the rule rather than the exception. Of 13 cases examined, only 4 (31%) had a normal diploid pattern. Nine (69%) had abnormal histograms, of which 3 (23%) were diploid-tetraploid, 3 (23%) tetraploid, 2 (15%) aneuploid, and 1 (8%) polyploid.

Although aneuploidy is commonly regarded as a sign of malignancy, this does not appear to be the case in CBPGs. Two of our patients had aneuploid tumors, yet, one (case 3) is alive and free of disease at 7 years and 7 months, while the other (case 5) died of histologically confirmed squamous cell carcinoma of the lung 2 years after removal of his CBPG. There was no evidence of recurrence of his carotid tumor.

Our single example of a malignant CBPG (case 9) was only serendipitously recognized as such when a small lymph node attached to the specimen was found to contain metastatic paraganglioma on histologic examination. This tumor was polyploid. Because of experiences such as this, Zbaren and Lehmann[16] advocate that all CBPGs should be excised with limited neck dissections to detect any possible lymph node metastasis.

The other patients with abnormal DNA histograms (cases 1, 6, 8, 11, and 12) have remained free of disease at follow-ups ranging from 2 to 28 years (average, 10.3 years; median, 6 years).

From the above-mentioned observations, we conclude that the DNA ploidy pattern of a CBPG cannot be used to assess malignant potential, at least in patients followed for an average of 7.3 years (median, 5.6 years). We must emphasize, however, that CBPGs are capricious tumors and that while metastases of many malignant CBPGs are evident either at or within 7 years of diagnosis,[12,16,34] some have not metastasized until 10 to 15 years or more after removal.[35,36]

Grignon et al[37] also observed that tumor ploidy could not be used as a diagnostic criterion of malignancy in their study of four paragangliomas of the urinary bladder. Three of their patients had aneuploid tumors and one had a tetraploid tumor. Two of the patients were alive and without progression at 2 and 7 years, respectively; one died of uncertain cause at 5 years; and one experienced multiple recurrences over a 22-year interval before developing metastases.

There have also been two recent studies on flow cytometric examination of adrenal pheochromocytomas with conflicting results. Amberson et al[38] analyzed 19 pheochromocytomas and found that 6 were diploid, 4 tetraploid, and 9 aneuploid. No tumor recurred over an average follow-up of 65 months. They also concluded that aneuploidy is not a specific marker of malignancy in adrenal pheochromocytomas. Hosaka et al[39] studied 75 pheochromocytomas of the adrenal glands and noted 23 to be diploid, 31 tetraploid-polyploid, and 21 aneuploid. None of their patients with diploid tumors followed for 10 years or more developed recurrences at metastases, whereas 31% of the tetraploid-polyploid tumors and 39% of the aneuploid tumors followed 10 years or more exhibited malignant behavior, the latter defined as either distant metastasis, local invasion, or local recurrence. In contrast to Amberson et al,[38] they concluded that flow cytometric DNA ploidy measurements provide useful prognostic information in patients with adrenal pheochromocytomas.

There is confusion in the literature, however, on what constitutes a malignant CBPG. We consider a tumor as malignant only if there is embolic spread to regional lymph nodes or more distant sites, usually to the lungs and bones. Direct extension into lymph nodes from nearby tumor does not qualify. Occasionally, CBPGs may infiltrate adjacent soft tissues or even the base of the skull and, in some instances, cause the death of the patient without evidence of metastases. Some regard these tumors as malignant[40]; we do not. We categorize such tumors as "locally invasive," even though they may be clinically malignant. Somewhere between 0% and 10% of CBPGs will recur following surgery.[7,11,12] This is not necessarily a sign of malignancy, but rather inadequate excision and tumor regrowth.

Care must also be taken not to confuse bilateral and multicentric paragangliomas for metastasis. According to Grufferman et al,[9] 4.4% of sporadic (nonfamilial) and 31.8% of familial CBPGs are bilateral. These may appear either synchronously or asynchronously. They also indicate that familial CBPGs are less likely to be malignant than nonfamilial tumors, the incidence being 2.5% in the former and 12% in the latter.

We, as others before us,[1,7,14,16,18,19,34] could find no relationship between mitotic activity, perineural invasion, or vascular invasion and clinical behavior. Perineural and vascular invasions were, however, observed only in tumors with abnormal DNA histograms; none of the diploid tumors exhibited these findings. There was also no correlation between nuclear pleomorphism and the identification of an aneuploid stem cell line. Of six tumors that contained numerous pleomorphic chief cells, two were diploid, two diploid-tetraploid, one tetraploid, and one polyploid.

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Evaluation of Mandibular Tumor Invasion With Magnetic Resonance Imaging

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• Evaluating the extent of tumor invasion of the mandible is clinically important in the management of mandibular tumors. Conventional imaging studies including panoramic radiography, bone scans, and computed tomography, as well as clinical evaluation can be unreliable in defining the extent of neoplastic marrow invasion. This study presents the initial UCLA, Los Angeles, Calif, experience with magnetic resonance imaging in evaluating mandibular invasion by benign and malignant neoplasms. Magnetic resonance imaging, using T_1 and T_2 images, was compared with conventional imaging methods in 11 patients with malignant lesions and nine patients with benign lesions. In all cases, magnetic resonance imaging most accurately determined the full extent of tumor invasion in the mandibular marrow spaces. Magnetic resonance imaging appears to be superior to offer clear benefits over conventional imaging methods, including computed tomography, for the evaluation of tumor invasion of the mandible.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:454-459)

The treatment of oropharyngeal tumors is in part greatly influenced by the degree of tumor invasion of the mandible. This can determine the type of resection performed and may indicate the form of reconstruction possible. Furthermore, radiographic imaging in the preoperative assessment of mandibular tumors appears necessary for rational planning of care. Current imaging methods available include conventional transmission radiography, panoramic radiography, bone scans, and computed tomography (CT), but each has significant false-positive and false-negative rates, making it difficult to use one test alone. Clinical evaluation can also be unreliable in defining the extent of mandibular involvement because surrounding inflammation may obscure the purported tumor margins. Whereas conventional imaging and clinical examination may reveal the extent of tumor involvement of the mandibular cortex, little specific information is gleaned as to marrow involvement. Computed tomographic scanning can give more detailed cortical resolution, but it is often hampered by ubiquitous dental work. Magnetic resonance imaging (MRI) is a new modality that has excellent soft-tissue and tumor tissue interface resolution. This study was initiated to assess if the limitations of conventional radiographic imaging techniques could be overcome by MRI. The role of MRI in determining the extent of man-

Histologic Diagnosis of Patients With Neoplasms

Tumors	No. of Patients
Malignant	
Squamous cell carcinoma	7
Alveolar ridge	2
Infratemporal fossa	2
Retromolar trigone	1
Floor of mouth	1
Tongue	1
Acute myelogenous leukemia	2
Plasmacytoma	1
Malignant schwannoma	1
Benign	
Ameloblastoma	3
Fibrous dysplasia	1
Hemangioma	1
Neurofibroma	1
Odontogenic keratocyst	1
Miscellaneous	
Osteomyelitis, osteradionecrosis	2

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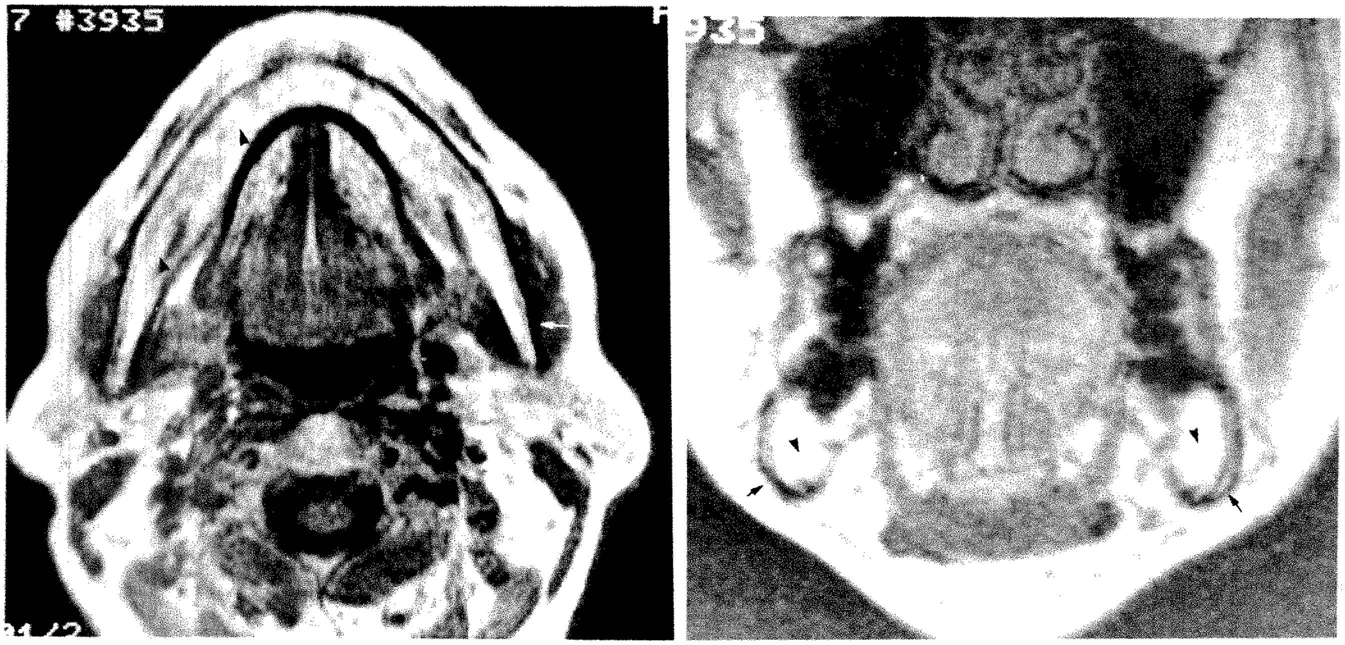

Fig 1.—Left, Normal magnetic resonance imaging. Axial plane, T_1 image. High signal from marrow (white) (arrowheads). Cortical bone is low signal (dark) (arrows). Right, Normal magnetic resonance imaging. Coronal plane, midbody mandible. High signal from marrow (white) (arrowheads). Cortical bone is low signal (dark) (arrows).

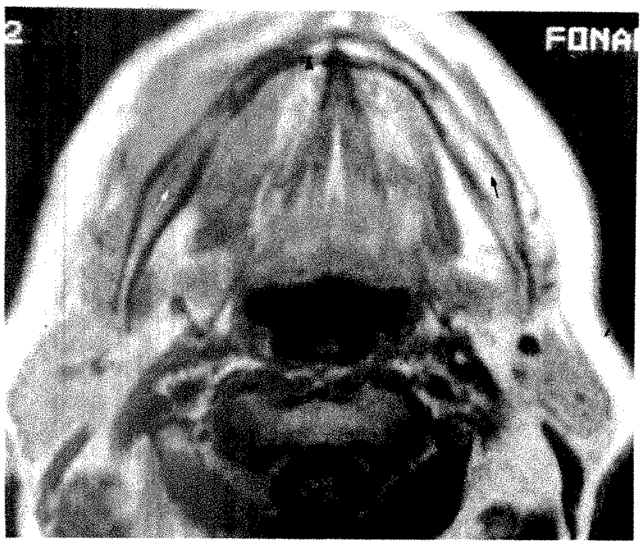

Fig 2.—Axial magnetic resonance imaging, T_1 image of alveolar ridge squamous cell carcinoma. High-signal marrow replaced by low-signal tumor (white arrow). Marrow is involved to symphysis (arrowhead). Normal marrow is shown on the left side (black arrow).

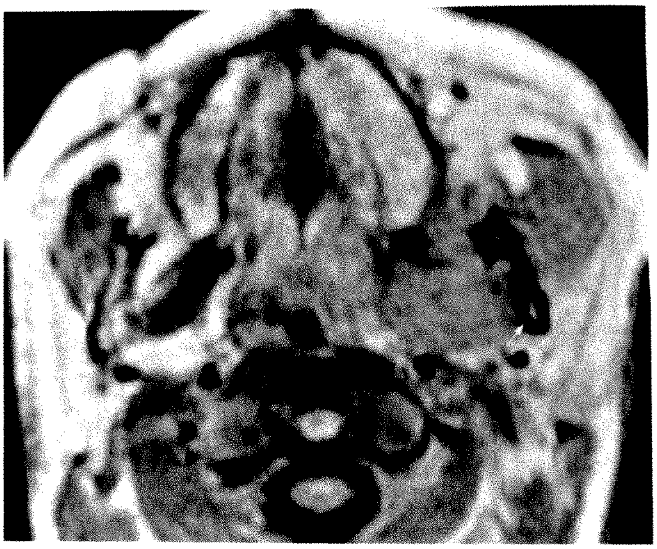

Fig 3.—Axial magnetic resonance imaging, T_1 image of squamous cell carcinoma of the infratemporal fossa. Invasion of low-signal tumor from infratemporal space along inferior alveolar nerve (arrowhead). The cortex is otherwise intact (arrow).

dible involvement by various types of tumors was examined and correlation was made with radiographic and pathologic findings.

MATERIALS AND METHODS

Twenty patients were selected for the study in a nonconsecutive manner from among all patients having MRI scans since 1986 at UCLA Center for the Health Sciences, Los Angeles, Calif. Two patients underwent concurrent CT and conventional imaging. All patients had anatomic or pathologic confirmation at open biopsy or surgical extirpation.

Magnetic resonance imaging was performed on either a 0.3-tesla permanent magnetic system (Fonar B-3000, Fonar, Melville, NY) or a 0.3-tesla iron core hybrid resistive system (Fonar B-3000M).

All scans were obtained with a 24-cm surface receiver coil placed about the mandible, as such a coil has been shown to be highly effective in defining tumor-bone margins.[1] The sections were 4 mm and 7 mm from center to center of sections. A 256 × 256 image matrix acquired through a 2-dimensional Fourier transform rapid spin echo technique was used. Images were

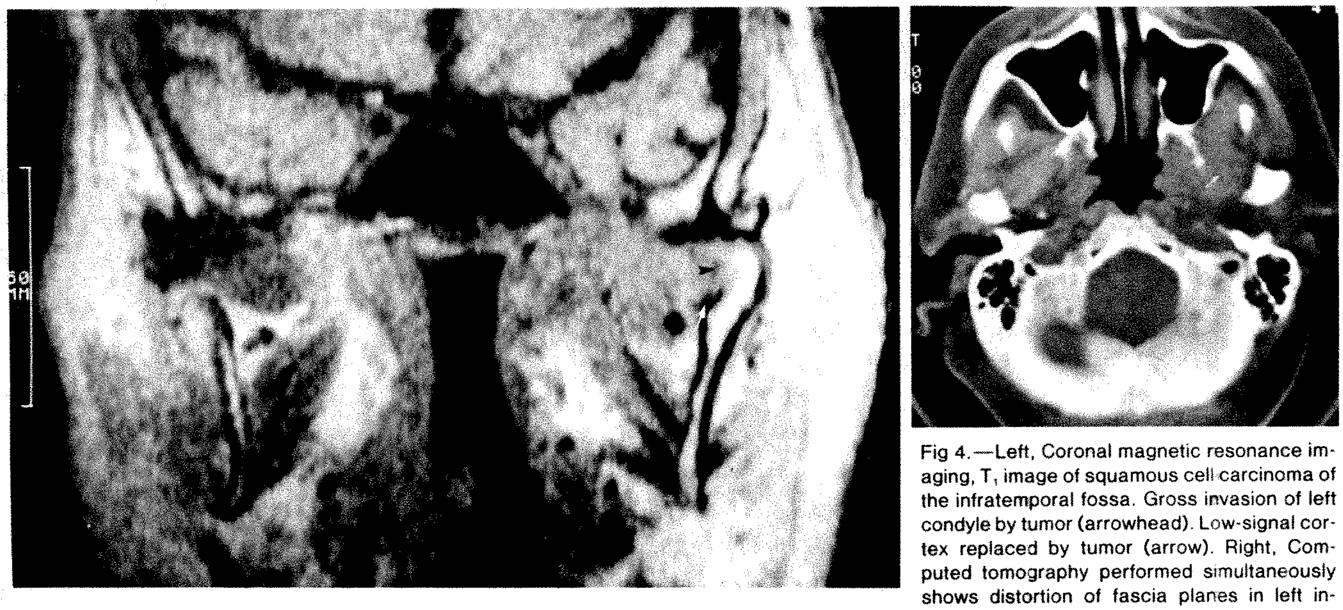

Fig 4.—Left, Coronal magnetic resonance imaging, T_1 image of squamous cell carcinoma of the infratemporal fossa. Gross invasion of left condyle by tumor (arrowhead). Low-signal cortex replaced by tumor (arrow). Right, Computed tomography performed simultaneously shows distortion of fascia planes in left infratemporal fossa (arrow). Bone of the condyle is intact.

acquired in the axial plane, with coronal and sagittal plane images where needed. Seven images were obtained in 10 minutes. T_1-weighted images with time to echo of 28 to 90 milliseconds and time to repeat of 500 to 2000 milliseconds were obtained. In selected cases, T_2-weighted images with time to echo of 56 to 84 milliseconds and time to repeat of 1500 to 2000 milliseconds were obtained.

RESULTS

The age range of the 20 patients in this study was from 17 to 74 years, 14 were male and 6 were female. The Table presents the final histopathologic diagnosis of the study patients. Representative illustrations are presented for particular lesions. For comparison, normal MRIs in the coronal and axial plane are also presented in Fig 1.

Group 1 includes seven histologically confirmed cases of squamous cell carcinoma. Two patients had involvement of the alveolar ridge, two patients had anaplastic squamous cell carcinoma of the infratemporal fossa, one patient had floor of mouth involvement, one patient had a retromolar trigone lesion, and one patient had tongue involvement. In T_1-weighted images, low-signal cortex (black) is replaced by high-signal tumor. Cases where T_1 images proved useful were in determining unexpected extension of tumor with marrow involvement when the overlying cortex appeared intact. This was important in this case of alveolar ridge cancer where the normally high-signal (white) marrow was replaced by tumor as far anteriorly as the symphyseal region, while the cortical margin (black) was preserved (Fig 2). Thus, MRI alerted the surgeon to perform a larger resection for a clinically unsuspected aggressive lesion. In a case of a carcinoma of the infratemporal fossa (Fig 3), invasion of the mandible along the inferior alveolar nerve is shown with clear demonstration of relatively high-signal tumor present at the foramen and invading along the nerve into the marrow space. The superiority of MRI over CT in imaging the infratemporal fossa is further demonstrated (Fig 4). Magnetic resonance imaging (Fig 4, left) shows replacement of high-signal marrow by low-signal tumor in the left condyle; a simultaneous CT (Fig 4, right) showed only distortion of tissue planes with no evidence of cortex invasion and no useful information as to the status of the bone marrow.

Four cases of nonsquamous cell carcinoma were also scanned. In two cases of acute myelogenous leukemia, MRI was useful in further staging the disease. Representative scans showing diffuse replacement of the bone marrow are demonstrated (Fig 5, left and top right). T_1 images (Fig 5, left) showed decreased signal, while increased signal was seen on T_2-weighted imaging (Fig 5, top right). The cortex can be easily seen and is preserved except in the left anterior body region. A panoramic radiography (Panorex) of this patient obtained at the same time showed only a 1.5-cm lytic lesion at the left canine tip (Fig 5, bottom right).

BENIGN LESIONS

The second group included nine patients with benign lesions of the mandible. Included in this group are three cases of ameloblastoma, and one case each of fibrous dysplasia, hemangioma, neurofibroma, odontogenic keratocyst, osteomyelitis, and osteoradionecrosis. In the cases of ameloblastoma T_1 scans clearly showed replacement of high-signal marrow by low-signal tumor, whereas the lesion and especially the cystic components appeared as high signal on T_2 images. A representative case is shown (Fig 6). A case of a large hemangioma of the lip was scanned with T_1 images revealing unexpected invasion of the bone of the symphyseal area by the tumor (Fig 7). Large feeding vessels are readily seen on T_1 images as flow void areas. A large neurofibroma of the mandibular ramus arising from the lingual nerve is

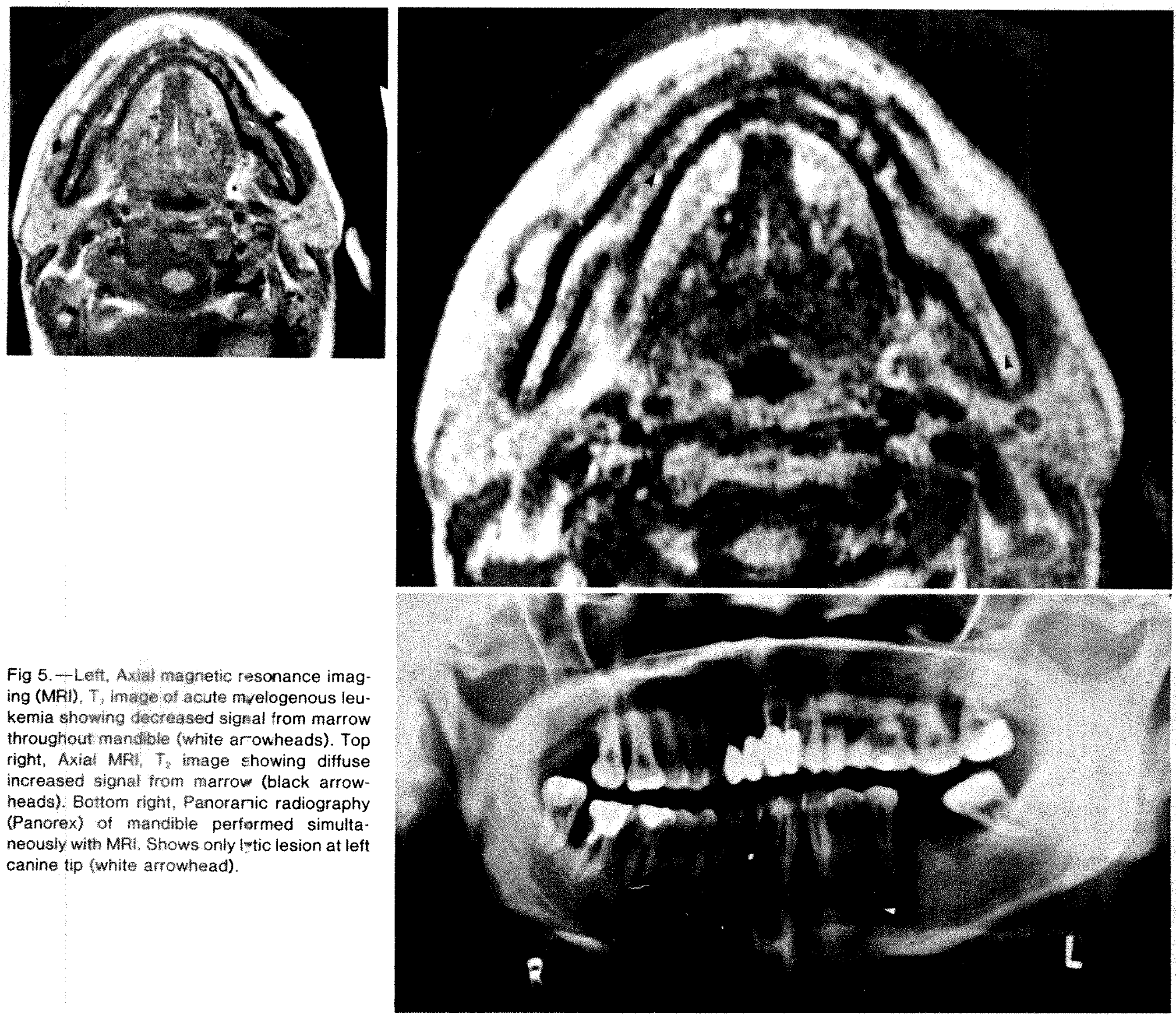

Fig 5.—Left, Axial magnetic resonance imaging (MRI), T_1 image of acute myelogenous leukemia showing decreased signal from marrow throughout mandible (white arrowheads). Top right, Axial MRI, T_2 image showing diffuse increased signal from marrow (black arrowheads). Bottom right, Panoramic radiography (Panorex) of mandible performed simultaneously with MRI. Shows only lytic lesion at left canine tip (white arrowhead).

presented (Fig 8). Intact cortex can be clearly seen although it is displaced by this tumor, emphasizing its benign nature. Cases of osteomyelitis, osteoradionecrosis, fibrous dysplasia, and odontogenic keratocyst were also scanned. In this last heterogeneous group, MRI was useful in establishing the diagnosis and extent obviating unnecessary extensive open procedures.

COMMENT

Determining the extent of tumor invasion of the mandible is critical to the successful management of oropharyngeal lesions. Accurate information allows for more thorough preoperative patient counseling and planning of tumor resection. For example, a tumor involving the anterior floor of mouth may require resection of the symphyseal area with its attendant morbidity. Preoperative scanning gives the head and neck surgeon more information regarding the amount of tissue needed for successful tumor extirpation and functional reconstruction. Reconstructive planning is also enhanced by having accurate preoperative information as to extent of tumor involvement, particularly if free flaps or large regional flaps are indicated.

Presently, there are four radiologic means for evaluating possible tumor invasion of the mandible. These are plain transmission radiography, panoramic radiography, bone scanning, and CT. However, each modality has its limitations. In a series of 150 patients undergoing mandibulectomy for invasive oral cancer, Weisman and Kimmelman[2] noted a 12% incidence of histologically proven invasion; of these one third did not have clinical evidence of tumor invasion into the mandible. It was also noted that routine mandible x-ray films had a 50% false-positive rate and a 5% false-negative rate. They concluded that use of routine x-ray films did not add significant new information to clinical patient evaluation. Other investigators[3] have also reported similar false-positive (40%) and false-negative rates (7%). These limitations are due to the fact that conventional x-ray films are inadequate in judging the extent of mandible tumor invasion.

To detect a visible, cancellous bone defect on plain x-ray film, a width of 75% must be eroded.[4] Panoramic radiography has a small increased sensitivity over conventional transmission radiography because of the absence of overlapping images. In an attempt to further increase the yield of diagnostic imaging studies, the use of bone scans was introduced. Baker et al[5] evaluated 25 patients with simultaneous panoramic radiography and bone scanning and in 4 cases (16%) they noted a normal panoramic radiography but positive bone scans. Gross invasion was found at surgery in only 2 of these cases (8%). Thus, bone scans also have a significant false-negative rate; indeed, when scans are systematically compared with radiographs, they fall far short of certainty.

Weisman and Kimmelman[2] compared the sensitivity and specificity of bone scans with plain radiography. They noted that bone scans had a false-positive rate of 53% and a false-negative rate of 12%. An even higher false-positive rate (67%) was noted in patients with large tumors. In addition, nearly all false-positives occurred in patients with anterior floor of mouth lesions, where it is most important to accurately establish invasion. They[2] concluded that bone scans are more sensitive than conventional x-ray films but have much higher false-positive rates and, thus, should be used in combination with other imaging modalities. The high number of false-positives seen with bone scanning has been attributed to various inflammatory diseases of the mandible including periodontal disease, old fractures, and osteomyelitis.[6]

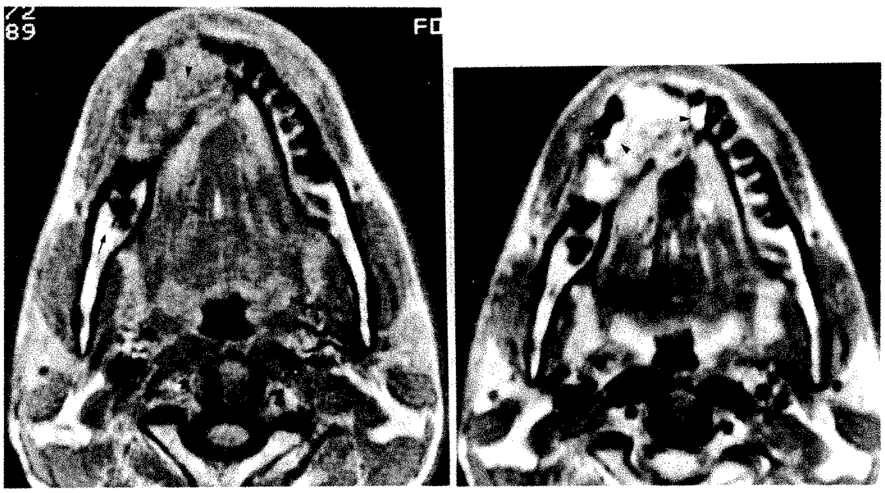

Fig 6.—Left, Axial magnetic resonance imaging, T_1 image of ameloblastoma showing high-signal marrow (arrow) replaced by low-signal tumor (arrowhead). Right, Axial magnetic resonance imaging, T_2 image showing high-signal enhancement of tumor with cystic areas (arrowheads).

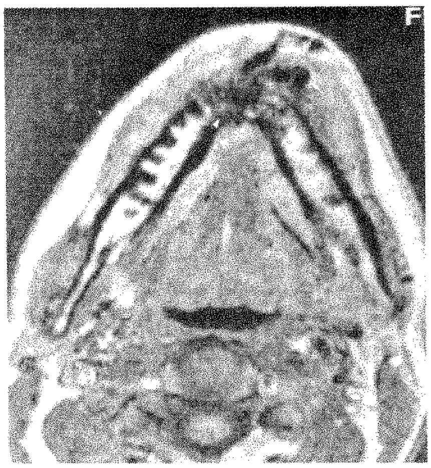

Fig 7.—Axial magnetic resonance imaging, T_1 image of hemangioma showing invasion of bone with replacement of low-signal cortex (arrowhead). Large feeding vessels are readily seen as flow voids (black) (arrows).

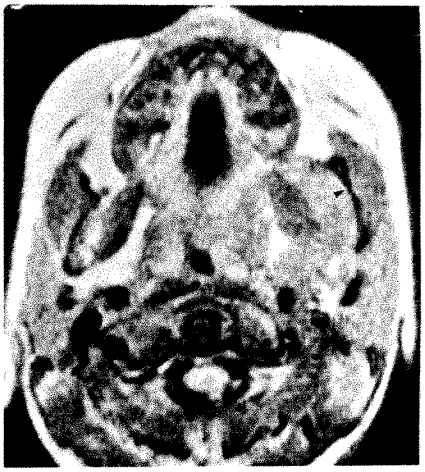

Fig 8.—Axial magnetic resonance imaging, T_1 image of neurofibroma showing displacement of left ramus secondary to tumor (arrowhead). No invasion of cortex is seen.

More recently CT has been advocated as an imaging technique for lesions of the mandible because of good bone detail and good soft-tissue definition. Close and coworkers[7] performed a prospective study of 43 patients with large (T_2 or larger) squamous cell carcinoma of the mandible. Using simultaneous CT scan and conventional intraoral and panoramic radiography, CT demonstrated histologically proven bone invasion in 11 of 11 patients, with only 1 false-positive. There were no false-negatives by CT examination. However, the authors[7] did point out the difficulties in using CT scans because of the large number of dental artifacts affecting the image both locally and throughout the imaged slice. Hence, whereas CT appears to be sensitive, it still has limitations as an imaging technique.

This study has shown several areas where MRI is superior to CT in terms of imaging the mandible for tumor involvement. These include determination of cortex involvement and evaluation of the bone marrow invasion. Several cases graphically illustrate these points. For example, the case in Fig 4 involved an aggressive squamous cell carcinoma of the infratemporal fossa. The CT showed a soft-tissue mass with tissue plane distortion in the left infratemporal fossa but no indication of bony involvement. In contrast, the MRI demonstrated extensive erosion of the medial portion of the temporomandibular joint, which had important implications regarding the type of resection and reconstruction used. In another case (Fig 5, left and top right) extensive involvement of the mandible by leukemic infiltrates was demonstrated by MRI. This demonstration of extensive, diffuse marrow involvement of the entire mandible with preservation of the cortex clearly evidenced the aggressive nature of the disease that required more extensive chemotherapy. In contrast only a 1.5-cm lesion at the left canine tip was visible by panoramic radiography (Fig 5, right).

Magnetic resonance imaging was of further diagnostic assistance in that several lesions have characteristic appearances on T_1- and T_2-weighted scans allowing confirmation of a clinically suspected diagnosis without the necessity of an open biopsy. For example, in the case of a hemangioma (Fig 7), information as to the caliber of vessels and hence, the probable histologic type of hemangioma is available because of the low-signal MRI produced flow voiding of moving blood in the vasculature. This may obviate the need for diagnostic angiography in selected cases.

In large part the advantages of MRI are due to the superior spatial resolution of the technique that allows discrete imaging of the cortex and adjacent marrow. Although the cortex itself is not directly seen, the relief image of the cortical bone with surrounding soft tissue clearly demonstrates both bony and soft-tissue structure. In addition, T_2-weighted MRIs effectively demonstrate the soft-tissue and tumor interface much more effectively than does CT. This is of importance because the margin of soft tissue between tumor and cortex is oncologically important in determining the extent of mandible that must be resected in squamous cell carcinoma. Marchetta et al[8] have demonstrated that when there is intervening normal tissue between a tumor and mandibular cortex, the probability of cortical involvement is low. Only with direct extension and invasion of the periosteum was the mandible involved in a series of 80 patients.[9] Hence, in those lesions not invading bone, conservative resections are feasible (eg, marginal resections of the mandible) without violating sound oncological principles. A further advantage of MRI is the ability to obtain images in any plane without the need to reposition the patient. This can be critical in getting satisfactory images with postoperative or debilitated patients. Future generation machines will be capable of obtaining scans in all planes simultaneously allowing shorter scan times. In addition, the absence of radiation exposure with MRI is of benefit since the average dose of radiation delivered for a CT scan is significant. Serial MRI scans, particularly for following lesions in children, are thus innocuous. Magnetic resonance imaging is also relatively unaffected by common metallic artifacts such as dental fillings, since only ferrous metals cause any significant image degradation due to magnetic field alterations around the metal. If an artifact is produced, it will generally be limited to the immediate area of the metal object with no degradation of the entire image.

Magnetic resonance imaging is superior to CT and other imaging modalities available for the mandible because of high soft-tissue spatial resolution and clear delineation of bone marrow and cortex. The addition of T_2 images allows improved detail of tumor margins and interface with surrounding normal tissue. The accurate prediction of tumor invasion permits better patient informed consent and preoperative planning for resection and reconstruction. Scanning in any image plane without repositioning is possible and images are relatively resistant to dental artifacts. This technology is in the early development stages as compared with the more mature CT techniques and, thus, rapid improvement in image resolution, quality, and acquisition speed can be anticipated. In time, MRI scans should become less expensive, making MRI highly cost-effective as an imaging modality for the mandible.

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Surgical Correction of the Snout Suffocation Syndrome

Vincent L. Keipper, MD, Peter G. Chikes, MD

• Two nursing home patients with difficulty breathing because of occlusion of the mouth and nares by an involuntary snout reflex–like mannerism have previously been described. In both cases advanced dementia, edentia, and a downward-angled nasal base were present. Life-threatening hypoxia occurred intermittently in one case, and after becoming severe, was corrected by the surgical procedure described.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:460-461)

Aging is associated with many physiologic and anatomical changes. Physicians caring for the elderly will be increasingly challenged by these alterations as the average age of their patients rises in the future.

In this case report, both an altered facial structure and abnormal brain function causing a snout reflex-like grimace in an elderly woman combined to cause dangerous difficulty in breathing. A simple surgical approach to correct this problem is presented.

REPORT OF A CASE

An 80-year-old woman was a resident in a skilled nursing home because of chronic dementia of the Alzheimer type. She was edentulous and had a history of a stroke with residual left hemiparesis and recurrent phlebitis. An electrocardiogram showed changes of an old inferior myocardial infarction, but no other cardiac history was known. She was not receiving any psychotropic medication.

Spells of difficulty breathing, poor responsiveness, cyanosis, and diaphoresis lasting several minutes were noted by the nursing staff. The respirations were described as "blowing," and the pulse and blood pressure were normal to slightly elevated. A physical examination, complete blood cell count, chemistry profile, electrocardiogram, and 24-hour Holter monitor recording were all unrevealing.

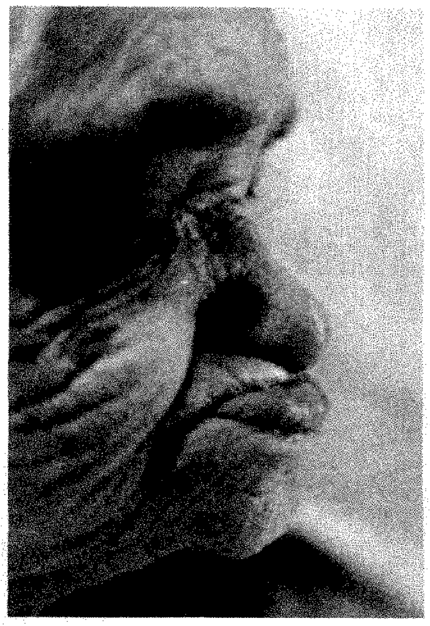
After several weeks of these spells occurring at intervals of hours to days, an observant nurse noted the patient would purse her lips and elevate her upper lip to occlude her nares, while her mouth remained closed. Air exchange was severely impeded (Fig 1). Lifting the nose tip upward would break the hypoxic episodes. A bridge of tape from the tip of the nose to the forehead would provide enough traction to prevent the spells.

These spells of "snout suffocation" continued for 2 years at infrequent intervals. Treatment with the tape bridge was used at those times; when the spells became more and more frequent, this caused skin breakdown at the tape sites and another means of control was sought. Dentures were considered, but the patient's worn gums and poor mental status prevented this approach. Long-term use of a nasopharyngeal tube was not thought to be feasible because of nasal and sinus complications, as well as being uncomfortable and unaesthetic. One of the authors, who was the patient's attending physician (V.L.K.), believed surgical intervention to be the best long-term approach and consulted the other author (P.G.C.) to perform corrective surgery.

SURGICAL PROCEDURE

External rhinoplasty would prevent airway obstruction by raising the drooping

Fig 1.—An 80-year-old woman with "snout suffocation" syndrome during one of her spells. The patient was supine when photographed.



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nasal tip. General anesthesia was necessary because of the mental status of the patient. After the patient's face was cleansed with multiple layers of povidone-iodine and draped as a sterile field, the nose at the level of the juncture of the upper and lower cartilages was anesthetized with 2% lidocaine (Xylocaine) with 1:100 000 parts epinephrine. In manipulating the nose, it was determined that the nasal tip needed to be rotated upward, shortening the length of the nose by 1.5 cm. Therefore, an ellipse of skin was outlined transversely across the nose, with the widest portion at the nasal dorsum measuring 1.5 cm. The skin ellipse was then excised. Hemostasis was obtained with electrocautery. Fat and subcutaneous tissue were removed both from the caudal portion of the upper cartilage and the cephalad portion of the lower cartilage. The cartilage was identified and found to be thinned. Portions of the caudal upper lateral and cephalad lower lateral cartilages were excised. The cartilages were then approximated with subcutaneous sutures of 4-0 polyglactin 910 (Vicryl), allowing the nasal tip to rotate cephalad. The subcutaneous layer was then closed with interrupted simple sutures of 4-0 polyglactin 910, and the skin was closed with 6-0 nonabsorbable monofilament. No dressing was placed, and no nasal packing was used because of the patient's tendency to keep her mouth tightly shut, even when it caused hypoxia.

RESULTS

The surgical wound healed with minimal deformity, and the nasal tip was rotated adequately to prevent obstruction of the nares when the upper lip was raised during the snout reflex-like maneuvers (Fig 2). Following the surgery, our patient had no more spells of snout suffocation and had no apparent side effects from the operation. Six months after surgery she died suddenly of a probable cardiac arrhythmia.

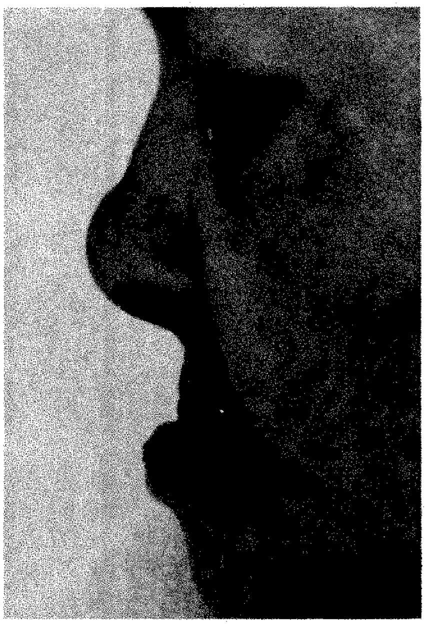

Fig 2.—The same woman (as in Fig 1) 1 month after surgery, also photographed while supine.

COMMENT

Our patient's problem was believed to be caused by a combination of a mobile upper lip associated with edentia and involuntary snout reflex-like movements. Part of this mannerism seems to involve a pursing of the lips tightly, thus blocking both the nasal and oral airways. Severe dementia with loss of frontal lobe function would seem to be a possible cause of this movement. For some unknown reason, the problem was episodic.

We do not believe this to be a unique situation. Two women with this problem were described in the same nursing facility.[1] In another report, five weak senile women with a poorly patent nose were noted to have spells of dangerous oronasal obstruction.[2] In the latter reference, high inspiratory pressure and weak oral structure were blamed for the nasal blockage, but the patients' refusal to open their mouths was unexplained. Perhaps this was also a result of poor frontal lobe function. That all of the cases involved women is interesting, but may be explained by selection bias due to the better longevity of women.

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William J. Wood, Jr, MD; S. Eva Singletary, MD; Robert C. Hickey, MD (*Arch Surg.* 1989;124:1374-1377)

Snoring Can Be Reduced When the Nasal Airflow Is Increased by the Nasal Dilator Nozovent

Björn Petruson, MD, PhD

• The ability to breath through the nose can be increased above normal by dilating the narrow nasal valve area with the plastic nasal device Nozovent. For 10 nights, 10 patients used Nozovent every other night, and the sleeping partners of the patients judged the snoring sound level using a snoring score. The results showed a significant decrease in snoring, from moderate to slight, when Nozovent was used, or from a barely tolerable to a tolerable noise level. In about 1 night out of 4, when the nostrils were dilated, the sleeping partners did not note any snoring at all. An increased nasal airflow is achieved with less negative intrathoracic pressure, which presumably results in less opportunities for vibrations of the soft palate.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:462-464)

The nasal valve area is the most narrow passage in the respiratory tract, causing more than half of the total resistance to nasal respiration in healthy subjects.[1] The proportional ratio between the cross-section area of the nasal valve and the bony piriform aperture is approximately 1:1.4.[2] The cross-section area on each side of the nasal valve is approximately 30 mm^2; in the middle of the nasal cavity, 120 mm^2; and in the nasopharynx, 150 mm^2 (Fig 1).

When the nostrils were dilated with the plastic nasal device Nozovent, the airflow through the nose increased, on the average, from 0.68 to 0.84 L/sec at 150 Pa, or 24%.[3] This improvement in airflow is comparable with that observed when nose drops are used for decongestion of the nasal mucosa in healthy subjects.[4] Nozovent thus improves nasal airflow so that it increases above normal, and it becomes much easier to breath through the nose. To see if nasal breathing could be improved during the night, 50 subjects used the dilator during a test period, and 40 (80%) of the 50 subjects noted that they slept better when using it. Some of the test subjects also found that they snored less than before. To evaluate the effect of Nozovent on snoring, 10 patients who snored regularly were tested.

PATIENTS AND METHODS

Patients

The study group consisted of 8 men and 2 women between 25 and 52 years of age (mean, 39 years) who, on the average, had been snoring for more than 8 years. When asked about the loudness of the snoring, 2 patients said their sleeping partner was awakened a couple of times during the night; 5, several times; and 3, continuously. Six patients snored in all sleeping positions. A slight septum deviation was observed in 3 patients, and 1 had a slightly narrowed nasal valve.

Nozovent

Nozovent is produced in a medical-grade plastic, which, after tests, has been accepted as a USP Cass VI Plastic by the Food and Drug Administration. The shape, which has been design patented, was formed and tested to fit in most Caucasian noses (Fig 2).

To prevent the dilator from falling out spontaneously, the end tabs are pressed against the skin in the lateral walls of the nasal vestibules, not against the vulnerable mucosa. The outsides of the end tabs are covered with knobs to increase friction, and the inferior parts of the tabs are shaped to fill the floor of the nasal vestibulum like a hook. When positioned in place for a couple of minutes, the pressure against the skin is accepted by most people like a watch is on the wrist (Figs 3 and 4).

During the day, Nozovent does not fall out spontaneously; during sleep, it might fall out when the nose is put into the pillow, which happens about 1 night in 5. By applying a plaster on the skin of the nostril from one side of the nose to the other,

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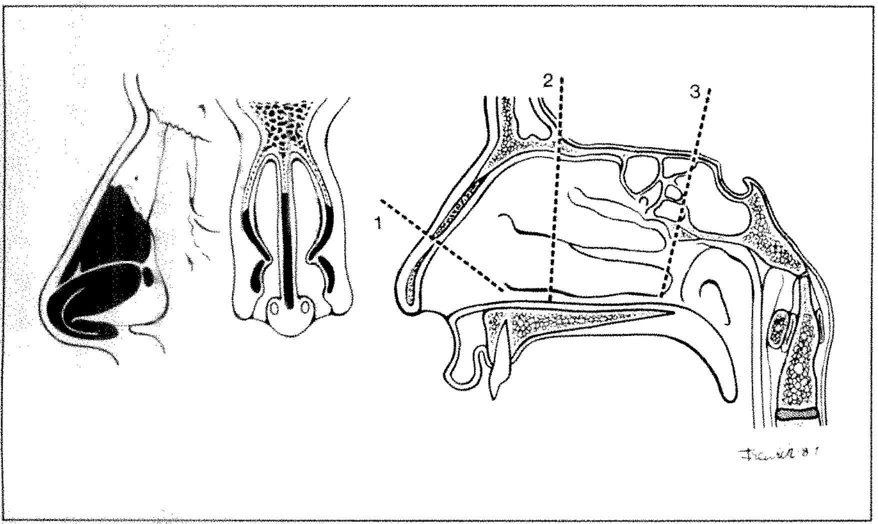

Fig 1.—The nasal valve area is the narrowest passage in the respiratory tract, with a cross-section area of approximately 30 mm² (1); in the middle of the nasal cavity, the area is about 120 mm² (2); and in the nasopharynx, it is approximately 150 mm² (3).

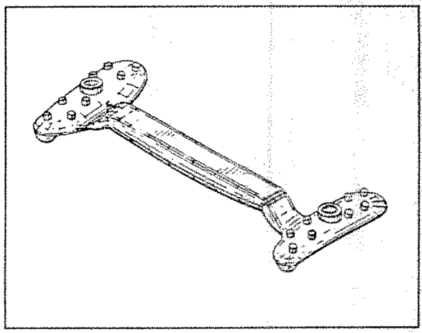

Fig 2.—Drawing of Nozovent.

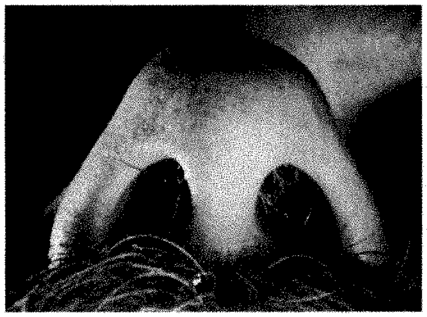

Fig 3.—A man's nose shown from below.

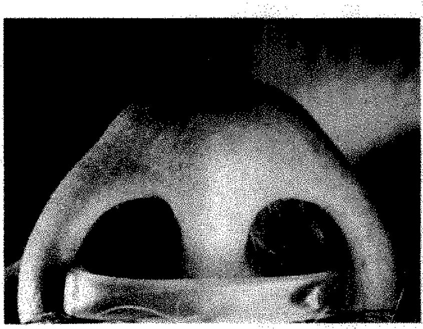

Fig 4.—The same nose seen in Fig 3 with a Nozovent in position.

alongside the bar of the dilator, a better fixation in the nose is achieved.

Snoring Score

After a training period of 1 week, the following 10 nights constituted the test period. Each of the 10 patients had to sleep every second night with the dilator, ie, 5 nights with it and 5 nights without it.

Every morning the patient had to consult the sleeping partner, and together they scored the snoring during the past night using a scale from 0 to 3 points (0, no snoring; 1, slight snoring; 2, moderate snoring; and 3, severe snoring). In all, 50 nights with and 50 nights without Nozovent were scored.

RESULTS

The total score for the nights when Nozovent was used was 45 points, and for the nights without it, it was 95 points, a highly significant difference ($P < .001$), which, on the average, means a decrease from moderate to slight snoring. The total score for each patient is shown in Fig 5.

When Nozovent was used, 14 out of 50 nights were slept through without the sleeping partner hearing any snoring, compared with 1 night without it. Without the dilator, severe snoring was noted during 12 nights vs 1 night with it.

All of the patients wanted to sleep with Nozovent in the future. In two patients it did fall out during rotation

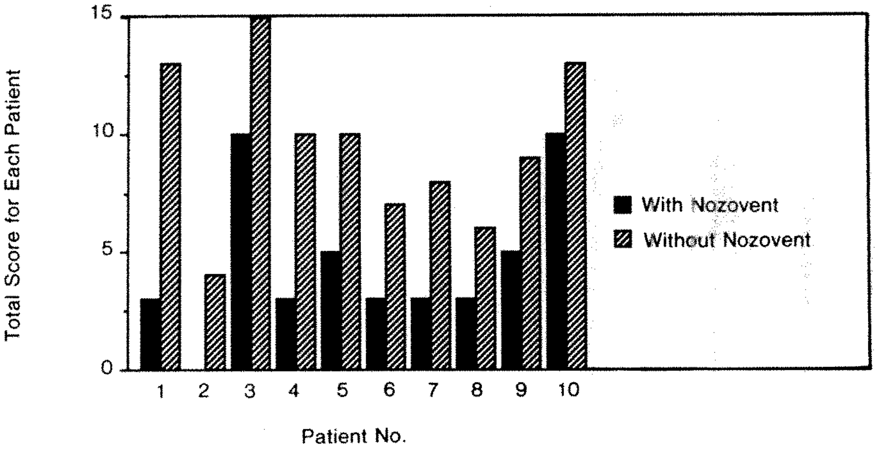

Fig 5.—The total snoring score for each of the 10 patients who slept 5 nights with and 5 nights without Nozovent. For each night the snoring score was as follows: 0, no snoring; 1, slight snoring; 2, moderate snoring; and 3, severe snoring.

in bed some of the nights and had to be put back into the nose when the patient woke up during the night.

COMMENT

Snoring can be very disturbing to a good social life. In the beginning, the nonsnoring partner in a relationship is the one who suffers the most from these nightly noises, but during the following years the snorer himself becomes aware of his snoring; he wakes himself up, gets a dry throat, and is sleepy in the morning. When the nasal breathing was increased above normal during the night by dilating the nostrils with Nozovent, some sleeping partners of pretest subjects noted less snoring than usual. In planning this study, it was decided to use the sleeping partners as judges of the snoring sound level. From a scientific point of view, a measurement in decibels would be preferable, but in social everyday life it is the opinion of the sleeping partner that is of most interest.

To make the testing period and the scoring as simple as possible, the snoring scale contained only four steps. The results from this study showed that, on the average, there was a decrease in snoring from moderate to slight with Nozovent, or, in other words, from a barely tolerable to a tolerable noise level. In about 1 night out of 4, when the nasal dilator was used, the sleeping partners did not note any snoring at all; ie, they were not disturbed in their sleep to the degree that they heard any snoring. Without Nozovent, no snoring was noted in only 1 night out of 50. On the contrary, severe snoring was more common during nights without the dilator: in 1 night out of 4 the sound was intolerable to the sleeping partner.

When the narrow nasal valve area is dilated by Nozovent, the airflow through the nose is increased above normal and less negative intrathoracic pressure is needed for inspiration. Presumably, in some cases, this lesser pressure is not sufficient to start the vibrations of the palate and soft tissues of the throat needed for generation of the snoring sounds. In other cases, when the vibrations start, the sound level seems to be lower.

Until now, the only efficient nonsurgical treatment for snoring has been the use of an airstream through the nose (continuous positive airway pressure).[5] When Nozovent is used, the airflow through the nose can be created by a less than normal negative pressure, which obviously is efficient in some, but not all, cases. As this therapy for snoring is new, further investigations have to be performed, and are in progress. So far, the dilation of the nostrils with Nozovent seems to be a simple and safe way to reduce snoring.

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ARCHIVES OF INTERNAL MEDICINE

Enalapril-Induced Cough

Gary R. Gibson, MD (*Arch Intern Med.* 1989;149:2701-2703)

Reduced Susceptibility to Syncope During Postural Tilt in Old Age

Lewis A. Lipsitz, MD; Elizabeth R. Marks, MS; Julia Koestner, BSN; Palmi V. Jonsson, MD; Jeanne Y. Wei, MD, PhD (*Arch Intern Med.* 1989;149:2709-2712)

Screening for the Multiple Endocrine Neoplasia Syndrome Type I

Hans F. A. Vasen, MD; Cornelis B. H. W. Lamers, MD; Cees J. M. Lips, MD (*Arch Intern Med.* 1989;149:2717-2722)

Characterization of a Chemotactic Defect in Patients With Kartagener Syndrome

Robert J. Walter, PhD; John R. Danielson, MD, PhD; Hernan M. Reyes, MD

• Kartagener syndrome (KS) is an autosomally inherited recessive condition characterized by situs inversus, bronchiectasis, and chronic sinusitis. Ciliary dynein, the mechanochemical force generator in ciliary movement, is deficient in patients with KS. We examined blood samples from two patients and tissue biopsy specimens from five patients and found: (1) no significant defect in neutrophil or monocyte chemotaxis in response to formylpeptide chemoattractant; (2) no alterations in centriolar structure, but significantly more centriole-associated microtubules in KS neutrophils and monocytes than in control leukocytes; and (3) a marked reduction in KS fibroblast chemotaxis in response to fibronectin compared with control fibroblasts. The significance of these cellular defects in KS is described.

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Kartagener syndrome (KS) is an autosomally inherited recessive condition characterized by situs inversus, bronchiectasis, and chronic sinusitis.[1-2] Estimates for the prevalence of this syndrome vary but it affects approximately 1 in 20 000 individuals in the general population. The situs inversus, a left to right mirror-image inversion of the thoracic and abdominal organs, may be complete or partial. The syndrome is frequently not diagnosed until the second or third decade of life when the bronchiectasis has reached a point where hospitalization may be required. Chronic inflammation of the upper respiratory tract may present as sinusitis or as a breathing, speech, or otologic problem. Patients are primarily treated symptomatically, with some requiring postural drainage to facilitate mucociliary clearance.

The pathogenesis of KS has been obscure until recent years when it was discovered that cilia and flagella from these patients lack the dynein side-arms normally associated with the ciliary A-tubules.[3,4] These side-arms are responsible for hydrolyzing adenosine triphosphate to adenosine diphosphate and transducing the energy released into the force used in bending cilia and flagella. Due to its absence, the cilia and flagella of these patients exhibit little or no motility. In patients with KS, mucociliary transport is deficient, males are sterile with immotile sperm, and females exhibit fertility problems that may be associated with dysfunctional oviductal cilia.[5]

Kartagener syndrome is a subgroup of the condition known as primary ciliary dyskinesia. This latter designation represents the most general classification of syndromes originating from structural defects of cilia. Primary ciliary dyskinesia is defined as any condition where ultrastructural defects in cilia are seen in conjunction with ciliary immotility or defective motility with or without situs inversus. Other types of ciliary defects falling under this same general classification include radial spoke deficiency,[6,7] ciliary microtubule transposition,[7] and missing or misaligned central singlet microtubules.[8] Each of these structural alterations also results in abnormal or reduced ciliary motility.

In KS, it is believed that forms of cell motility other than ciliary and flagellar movement may also be affected by the dynein deficiency and that these effects may be related to the clinical manifestations seen in KS. Indeed, other motility-related defects have also been reported in patients with KS (Table 1). These include decreased neutrophil random locomotion[9-11] and chemotaxis[9,11-14] as well as decreased in vitro skin fibroblast random locomotion.[15] The studies presented herein provide further information about chemotaxis in neutrophils, new findings on monocytes and fibroblasts, and also an assessment of the leukocyte microtubule cytoskeleton in patients with KS.

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PATIENTS, METHODS, AND MATERIALS

Patients and Biopsy Methods

Patients with clinically confirmed KS exhibiting situs inversus and a history of bronchiectasis, chronic upper respiratory tract infection, and otitis media were studied. Samples from age-matched control subjects (n = 10) free of clinical symptoms were also examined. For venipuncture, 10 to 15 mL of blood was drawn into heparinized tubes and leukocytes were isolated as described below. Skin biopsy specimens were obtained by removing a full-thickness punch of skin through the dermal level from the medial forearm. This punch was taken aseptically using local anesthesia (subcutaneous 1% lidocaine without epinephrine). Biopsies of ciliated nasal epithelium were performed on patients with KS and on healthy volunteers using a sharp ear curette introduced onto the middle turbinate through the nose. Nasal ciliary biopsy specimens were placed in *N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid (HEPES)-buffered salt solution (see below) and examined using phase contrast microscopy or were fixed immediately and prepared for electron-microscopic examination as described below. Nasal cilia from patients with KS showed little or no motility when viewed in the light microscope, whereas those of control donors displayed vigorous movement. Results from studies of five separate patients with KS are presented; five KS fibroblast cell lines and blood samples from two patients with KS were studied. Blood samples from other patients with KS were not available. All subjects lacked active respiratory tract infection and were taking no medications (Table 2).

Cell Culture Conditions

Skin explants from punch biopsy specimens were diced, suspended in culture medium, and placed into 35-mm culture dishes. Fibroblasts were maintained in continuous culture in Dulbecco's modified Eagle's medium supplemented with double-strength amino acids, double-strength glutamine, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and 10% fetal calf serum and were used between passage numbers 8 and 18. Cells were maintained at a pH of 7.2 in a water-jacketed carbon dioxide incubator at 37°C and harvested from flasks using 0.1% trypsin with 0.2 mmol/L of ethylenediaminetetraacetic acid. They were centrifuged at 500*g* for 5 minutes, resuspended in fresh medium, counted using a hemacytometer, and then loaded into chemotaxis chambers. Cultures were stained for mycoplasma using 2,2(4 - hydroxyphenyl) - 6 - benzimidazolyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (Hoechst 33258) and examined using fluorescence microscopy,[16] but no mycoplasmas were detected.

Table 1.—Cellular Defects in Kartagener Syndrome

Defect	Cell Type	References
Dynein arm deficiency, inner and/or outer arms	Sperm, respiratory tract, fallopian tube	3-5
Reduced ciliary motility	Respiratory epithelium	30
Altered random motility	Polymorphonuclear leukocytes	9-11
Decreased random motility	Fibroblasts	15
Reduced chemotaxis	Polymorphonuclear leukocytes	9,11-14
Decreased centriolar microtubules	Polymorphonuclear leukocytes	12
Decreased intramembranous particles on plasma membrane	Polymorphonuclear leukocytes	14
Reduced magnesium, adenosine triphosphatase	Respiratory epithelium	31

Table 2.—Characteristics of Patients With Kartagener Syndrome Studied*

Patient	Number	Sex of Donor	Age of Donor, y	Cell Passage
1	715	F	21	16
2	685	F	6	18
3	206†	M	10	12
4	120†	F	19	15
5	214	F	18	8

*F indicates female; M, male.

†Patients from whom blood samples for neutrophil and monocyte chemotaxis studies were obtained.

Leukocyte Isolation

Neutrophils and mononuclear leukocytes were isolated from venous blood. Erythrocytes were sedimented at 1*g* in 1.25% dextran (pyrogen free) and the leukocyte-rich plasma was drawn off. Two milliliters of plasma was diluted with an equal volume of buffer containing 140 mmol/L of sodium chloride, 10 mmol/L of potassium chloride, 10 mmol/L of HEPES, 5 mmol/L of glucose, and 2 mg/mL of bovine serum albumin (HEPES-buffered salt solution, pH 7.4) and layered onto 1 mL of buffered metrizamide (lymphocyte separation medium). This discontinuous gradient was centrifuged at 500*g* for 5 minutes at room temperature. The mononuclear cells at the interface were removed and the neutrophil pellet resuspended. The neutrophils were rinsed in HEPES-buffered salt solution containing 2 mmol/L of ethylenediaminetetraacetic acid, and contaminating erythrocytes were lysed by hypotonic shock. The mononuclear fraction was diluted with 5 mL of HEPES-buffered salt solution containing 2 mmol/L of ethylenediaminetetraacetic acid and 2.5% dextran and centrifuged for 5 minutes at 500*g*. The platelet-rich supernatant was aspirated off and the washing procedure repeated on the resuspended cell pellet. Cells were resuspended in HEPES-buffered salt solution containing 1 mmol/L of magnesium chloride and 0.2 mmol/L of calcium chloride, counted using a hemacytometer, diluted to 4×10^5 cells per milliliter, and loaded into chemotaxis chambers.

Chemotaxis and Chemokinesis Measurements

Fibroblasts harvested by trypsinization were suspended in serum-free HEPES-buffered Dulbecco's modified Eagle's medium (10^6 cells per milliliter). Affinity-purified bovine serum fibronectin was selected as the chemoattractant, since fibronectin is normally synthesized by fibroblasts in vitro and in vivo, where it functions both as a cell-substrate attachment factor and as a chemotactic agent.[17] This compound is involved in embryogenesis, inflammation, and wound healing.[18] Fibronectin (0 to 12 μg/mL) in HEPES-buffered Dulbecco's modified Eagle's medium was placed into lower wells of a 48-well chemotaxis chamber (Neuroprobe, Cabin John, Md). A polyvinylpyrrolidone-free polycarbonate filter (Nucleopore, Pleasanton, Calif) with 5-μm pores was pretreated with 0.001% poly-L-lysine for 10 minutes, rinsed, dried, and placed over these lower wells. Suspended fibroblasts (25 μL; 25 000 cells) were placed into the upper wells and either additional media or media with fibronectin was also added (25 μL). Chambers were then incubated at 37°C in a humidified

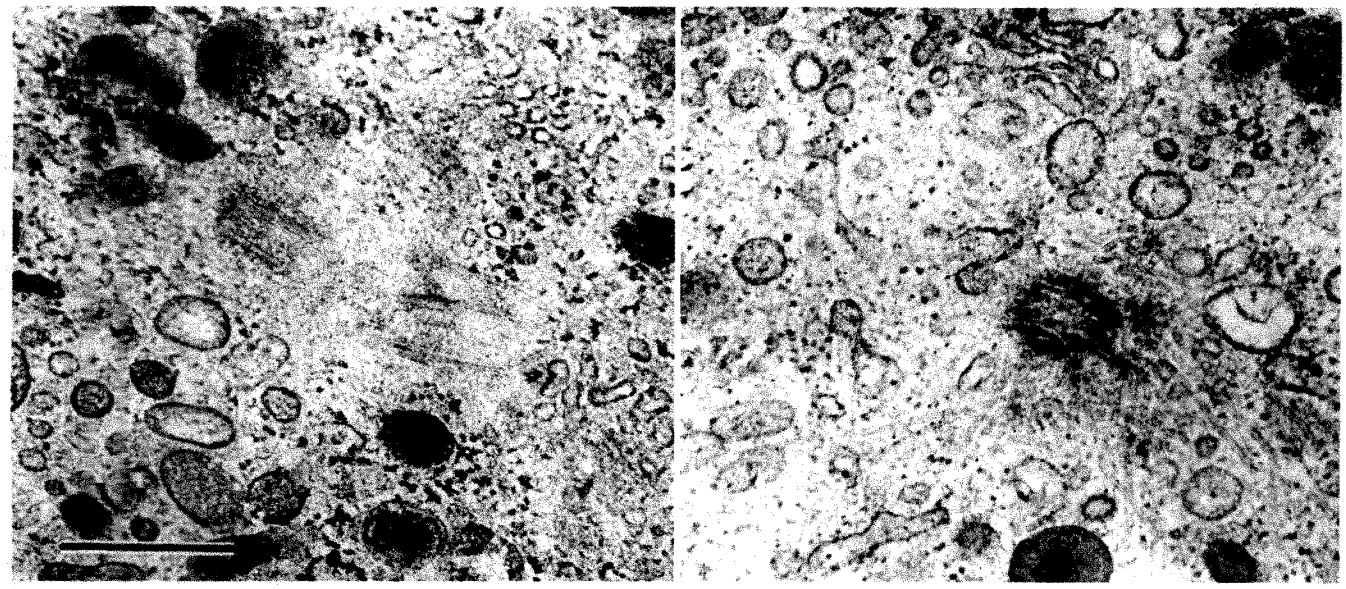

Fig 1.—High magnification electron micrographs of centriole pair from normal (left) and single centriole from Kartagener syndrome (KS) (right) neutrophils showing centriole-associated microtubules. Note the large number of microtubules in the neutrophils from patients with KS compared with the number seen in the neutrophils from control subjects (magnification bar, 0.5 μm).

incubator for 4 hours. This incubation was terminated by removing the filter from the chamber, fixing it in methanol, scraping the adherent, nonmigrated cells off the top of the filter, and staining the migrated cells on the underside of the filter with Lillie's hematoxylin. Filters were then dried onto glass slides, mounted, and cell nuclei counted at ×400 magnification. Samples were run in triplicate and five microscope fields in each well were counted.

For leukocyte chemotaxis studies, formyl-methionyl-leucyl-phenylalanine was chosen as the chemotactic agent. Formyl-methionyl-leucyl-phenylalanine is a potent chemoattractant that is a synthetic analog of a naturally occurring bacterial peptide.[19] Similar or identical peptides are released by bacteria infecting human wounds.[20] Formyl-methionyl-leucyl-phenylalanine was placed into the lower wells of the multiwell chemotaxis chamber and purified neutrophils or monocytes were loaded into the upper wells (25 μL; 20 000 cells). Filters were not pretreated with poly-L-lysine and assays were run for 2 hours at 37°C.[21,22]

Electron Microscopy and Microtubule Counts

Nasal epithelium biopsy specimens were fixed in 3% glutaraldehyde, 4% tannic acid, 0.1 mol/L of cacodylate, at a pH of 7.4 for 3 hours at room temperature. Tissue samples were then rinsed, postfixed in 1% buffered osmium tetroxide, dehydrated, sectioned, and stained. Electron micrographs confirmed that cilia from patients with KS partially or totally lacked inner and outer dynein side-arms.

Pellets of purified monocytes or neutrophils were fixed in 1% glutaraldehyde, 1% paraformaldehyde in 0.075 mol/L of cacodylate buffer, at a pH of 7.2 at room temperature for 1 hour. These specimens were then postfixed in 1% osmium tetroxide for 30 minutes, dehydrated in ethanol series, embedded in epoxy resin (Epon 812), sectioned, and stained with uranyl acetate-lead citrate.[23] Sections were examined and photographed using an electron microscope (JEOL 100S).

For microtubule counts, cells displaying one or both centrioles in a given section were photographed at ×40 000, and the number of microtubules counted within a 4 μm^2 area centered on the centriole(s). Twenty-five neutrophils and 25 monocytes from each patient with KS and from each control were examined. Photography and quantitation were performed in a blinded fashion.

Statistical Analysis

For all chemotaxis data, assays were run in 2 to 5 separate experiments and at each chemoattractant concentration triplicate wells were counted. The means of cell counts from triplicate wells were compared for control and KS groups using paired or mean t tests. For microtubule counts, mean microtubule numbers from control and KS leukocytes were also compared using t tests.

RESULTS

Centrioles from leukocytes of patients with KS (Fig 1) showed no apparent alterations compared with those from control subjects. However, counts of centriole-associated microtubules revealed that the numbers of microtubules in KS leukocytes were elevated (Table 3). Kartagener syndrome neutrophils showed an average of 62% more microtubules than did control neutrophils ($P < .05$) and KS monocytes had 41% more microtubules than did control monocytes ($P < .05$).

Multiwell micropore chemotaxis assays were performed to ascertain the migratory capabilities of leukocytes and fibroblasts from patients with KS. The chemotactic response of neutrophils from control subjects and from patients with KS to formylpeptide at three different concentrations was examined (Fig 2). At each concentration of chemoattractant used, a consistently greater chemotactic response is seen in the neutrophils from patients with KS than in the neutrophils from control subjects. These differences, however, were not statistically significant. The chemotaxis of monocytes from control subjects and from patients with KS was also compared (Fig 3) and was found to be similar.

Figure 4 shows the results of chemotaxis assays of cultured fibroblasts grown from skin biopsy specimens taken from control subjects and from patients with KS. These cells re-

Table 3.—Counts of Centriolar Microtubules From Control and Kartagener Leukocytes*

Patient Group	Patient	Microtubule Counts (Mean ± SD) Neutrophils	Microtubule Counts (Mean ± SD) Monocytes
Control	1	19.9 ± 4.6	22.4 ± 5.4
	2	22.2 ± 6.1	23.9 ± 4.9
	3	21.6 ± 5.3	25.8 ± 6.3
	4	23.7 ± 6.3	23.2 ± 8.4
	5	23.0 ± 3.5	26.9 ± 7.0
	Mean ± SEM	22.1 ± 0.6	24.4 ± 0.8
Kartagener syndrome	1	26.4 ± 4.8	43.8 ± 6.8
	2	47.1 ± 7.2	28.2 ± 3.9
	Mean ± SEM	36.7 ± 10.3†	36.0 ± 7.8†

*For microtubule counts, cells displaying one or both centrioles in a given section were photographed at ×40 000, and the number of microtubules counted within a 4-μm^2 area centered on the centriole(s). Twenty-five cells from each patient with Kartagener syndrome and from each control subject were examined.

†$P < .05$ compared with control group.

sponded to chemotactic gradients of fibronectin. Fewer fibroblasts migrated compared with leukocytes, but this is as expected since fibroblasts are known to locomote at a much slower rate than do leukocytes. Chemotaxis was reduced by 34% at 1.5 μg/mL, by 47% at 6.0 μg/mL, and by 48% at 12 μg/mL of fibronectin. All of these reductions were statistically significant ($P < .02$) when compared with fibroblasts from normal age-matched control subjects at similar culture passages.

COMMENT

In this study, we examined tissue samples from a total of five patients with KS and several control subjects to ascertain the extent of the cellular defect expressed in KS. Ciliary dynein was deficient in both patients, but no significant difference was seen in neutrophil or monocyte chemotaxis in response to formylpeptide chemoattractant. Further, no alterations in centriole structure were observed, but a significant increase in the number of centriole-associated microtubules was observed in KS neutrophils and monocytes. Finally, the chemotaxis of KS fibroblasts was markedly reduced compared with control fibroblasts.

The ciliary dynein deficiency found in patients with KS is believed to be responsible for the reduction or absence of ciliary motility seen in these patients.[3,4] This ciliary immotility is believed to be the underlying cause of all the clinically manifested symptoms of this syndrome. A great number of malformations or diseases have been catalogued in the KS population,[2] but most of these are no more frequent than in the general population and are probably unrelated to the underlying cause of KS. However, bronchiectasis, sinusitis, otitis media, reproductive abnormalities, and situs inversus are common in KS and almost certainly due in some measure to ciliary immotility.

Alterations in leukocyte function in patients with KS might significantly reduce their ability to resist respiratory infections. Leukocyte adherence, phagocytosis, bacterial killing, lysosomal enzyme release, chemiluminescence, and random motility have been studied and were found to be normal.[12,14] However, neutrophil random motility and chemotaxis have also been examined and found to be altered or reduced by some investigators.[9,10,12,14] Such alterations could compromise the immune response to infection resulting in increased frequency and severity of infection. In this study, we have observed no significant reduction in the chemotactic response of KS neutrophils or monocytes to formylpeptide chemoattractant. This finding may be related to the small KS sample size or may indicate that the chemotaxis defect is specific for the chemoattractant used. Similarly, Escudier et al[24] and Corkey et al[25] reported normal or elevated neutrophil chemotaxis in response to bacterial formylpeptide. In most of the studies where a chemotaxis defect was observed, activated serum

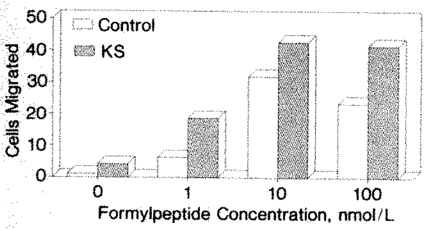

Fig 2.—Chemotaxis of neutrophils from two patients with Kartagener syndrome (KS) and five control subjects in response to formylpeptide at three different concentrations (1, 10, and 100 nmol/L). The number of cells observed per high-power field (×400 magnification) was counted. Samples were run in triplicate wells and five fields from each well were counted and averaged for each subject at each concentration of formylpeptide. Although KS neutrophils consistently exhibited greater chemotaxis, no statistically significant differences were noted.

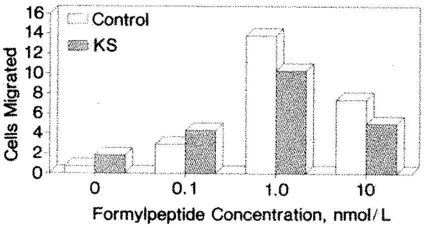

Fig 3.—Chemotaxis of monocytes from two patients with Kartagener syndrome (KS) and five control subjects in response to formylpeptide at three different concentrations (1, 10, and 100 nmol/L). The number of cells observed per high-power field (×400 magnification) was counted. Samples were run in triplicate wells and five fields from each well were counted and averaged for each subject at each concentration of formylpeptide. No statistically significant differences were found.

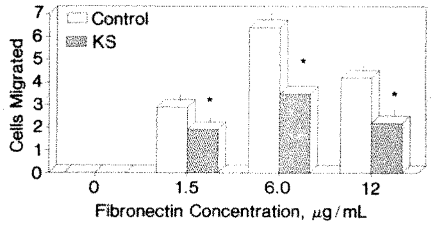

Fig 4.—Chemotaxis of cultured fibroblasts from five patients with Kartagener syndrome (KS) and five control subjects in response to fibronectin. The number of cells observed per high power field (×400 magnification) was counted. Samples were run in triplicate wells and five fields from each well were counted and averaged for each subject at each concentration of formylpeptide. Standard errors of the mean are shown as bars, and asterisks indicate KS groups that differ significantly ($P < .02$) from controls.

was used as the chemotactic stimulus. Thus, it seems that KS leukocytes may respond poorly to serum chemoattractants but normally to formylpeptide.

Microtubules are believed to function in imparting directionality to cell locomotion.[26] Reductions in microtubule numbers (as with colchicine) or alterations of microtubule-associated proteins (such as dynein or microtubule-associated protein 1C) may diminish chemotactic responsiveness. When KS neutrophils and monocytes are compared with leukocytes from control subjects, microtubule counts indicated significantly increased numbers of microtubules in KS leukocytes. This runs counter to data trends reported by Afzelius et al,[12] although no statistically significant differences were shown in that study. Further, the microtubule counts reported in that study were extremely low for all groups, suggesting that microtubules may have been lost during fixation and subsequent preparation, or not visualized due to excessive section thickness. The increased microtubule numbers observed herein may be a compensatory mechanism correcting for deficient dynein or other microtubule-associated proteins.

Since microtubule numbers were altered in KS leukocytes, and KS fibroblast chemotaxis was noticeably reduced compared with that of control subjects, the KS defect apparently is expressed even in non-ciliated somatic cells.[15] Such a cellular defect could be accounted for in two possible ways. (1) Dynein is deficient in these somatic cells. Thus, cellular activities ordinarily requiring dynein would be inhibited in its absence. Dynein has only recently been found in somatic cells but its functions in these cells remain hypothetical.[27,28] (2) Dynein deficiency does not account for all cellular defects in KS. A second, unknown alteration may be responsible for the chemotactic defect in fibroblasts and the microtubule alterations in leukocytes. Qualitatively, the microtubule cytoskeleton and microtubule-associated proteins of KS fibroblasts appear identical to control fibroblasts,[15] but certain species of high-molecular-weight proteins (perhaps dynein or kinesin) may be deficient in these cells.[15,29] Such a deficiency may be pivotal in generating the cellular defects and eventually the clinical manifestations seen in KS. Further work in characterizing these proteins and elucidating their functions is currently in progress.

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Facial Reconstruction for Radiation-Induced Skin Cancer

William R. Panje, MD, Thomas J. Dobleman, MD

• Radiation-induced skin cancers can be difficult to diagnose and treat. Typically, a patient who has received orthovoltage radiotherapy for disorders such as acne, eczema, tinea capitis, skin tuberculosis, and skin cancer can expect that aggressive skin cancers and chronic radiodermatitis may develop subsequently. Cryptic facial cancers can lead to metastases and death. Prophylactic wide-field excision of previously irradiated facial skin that has been subject to multiple recurrent skin cancers is suggested as a method of deterring future cutaneous malignancy and metastases. The use of tissue expanders and full-thickness skin grafts offers an expedient and successful method of subsequent reconstruction.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:470-474)

Patients with facial skin cancer that usually develops many years after exposure to superficial ionizing radiation can often develop multiple recurrences. Unlike isolated basal cell cancers that arise in nonirradiated skin, cutaneous cancer that originates in previously irradiated skin tends to be difficult to detect. Delay in tumor identification can lead to metastases and death. Skin cancer can be multifocal and difficult to identify clinically by both the patient and/or the physician. Once regional or distant metastases occur, the cure rate drops from 85% to less than 25%. These facts suggest that, in select cases, consideration should be given to preventive surgery. Since radiation-induced facial malignancies arise predominantly in the previously irradiated skin areas, it may be prudent to select high-risk patients for early removal of the "condemned skin."

We have developed a technique of removing the entire condemned epidermis and using tissue expanders and a full-thickness skin graft to resurface the nose and middle aspect of the face.

We recommend that some patients who develop multiple recurrent skin cancers as a result of prior radiation therapy of the face be considered for total skin excision for prevention of further recurrences, possible metastases, and death.

PATIENTS AND METHODS

We reviewed the charts of seven patients who had received radiation therapy to the face and who were subsequently evaluated by the senior author (W.R.P.) in order to determine which patients might benefit from prophylactic excision of facial skin to prevent subsequent development of integument cancers. All seven patients were referred to us after having had multiple facial skin cancers that were treated primarily with surgery directed at removal of the biopsy-proved malignant lesions. Other forms of treatment, including cryotherapy, megavoltage radiation therapy, and topical chemotherapy with agents such as fluorouracil, were also used in an attempt to eradicate the cancers.

The clinical courses of the patients are described in the "Report of Cases" section as an illustration of the disastrous consequences of waiting until the cancer manifests itself. The technique of total facial reconstruction with expanded, nonirradiated skin and full-thickness skin grafting utilized for the seventh patient, is described as a method for replacing facial skin at high risk for developing skin cancer.

REPORT OF CASES

Case 1.—A 74-year-old man who had undergone facial radium treatments for acne at 18 years of age was referred to W.R.P. for facial reconstruction. His first facial skin cancer (basal cell carcinoma) had developed at the age of 38 years. Since then, he has had more than 150 operations for facial cancer. He has lost essentially all of his nose, upper lip, palate, and most of one ear. His right eyelids were removed and reconstructed. He suffers from diplopia because of periorbital fibrosis resulting from secondary scarring associated with his multiple operations. He has had several operations for reconstruction of his upper lip and alveolus. He still requires special eyeglasses, and he cannot wear a facial prosthesis. He continues to have new skin cancers in previously irradiated areas of the face.

Case 2.—A 68-year-old man received an unknown dose of orthovoltage radiation therapy to the face and lips for acne vulgaris at the age of 18 years (Fig 1, left). Because of his occupation as a farmer, his face also had excessive exposure to actinic damage. He has had multiple basal cell cancers and actinic keratoses excised from the face, nose, and lips. A 2.5-cm basosquamous cell carcinoma of the lower lip was removed when he was 65 years old. He subsequently developed a large mass on the left side of the neck. A biopsy of the cervical mass showed that it was a metastatic well-differentiated squamous cell carcinoma. Despite aggressive radiation therapy and surgery, the patient succumbed to this cancer.

Case 3.—A 39-year-old woman had received facial irradiation at 16 years of age for pustular acne vulgaris (Fig 1, right). She had 42 excisions of facial basal cell and basosquamous cell cancers, mainly involving the lips. Extensive radiation fibrosis, as well as surgical cicatrix formation, produced a severe labial deformity. She recently developed an extensive squamous

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cell carcinoma of the lips. Although she received radiation therapy and chemotherapy, she continues to have recurrent cancer. She refuses any form of surgical treatment.

Case 4.—A 59-year-old woman with a history of radiation treatment for acne as a child had severe midfacial mutilation that resulted from multiple local excisions of gross, persistent cancer. She had curative radiation therapy to the face, but it did little to retard the advancement of the malignant lesions. Her medical history was unremarkable except for her childhood radiation therapy. Physical examination showed gaping defects in both cheeks and she had only one eye. Pathologic examination revealed adnexal basosquamous cell carcinoma.

Case 5.—A 76-year-old woman had developed a severe contact dermatitis of the face in the 1940s, and was treated with radiation in an effort to stop the progression of this disorder. From 1962 to 1985, she had more than 100 local excisions for recurrent basal cell and basosquamous cell carcinoma. Her medical history was otherwise unremarkable. On physical examination, chronic radiodermatitis of the face was evident, along with multiple facial surgical scars. She had ectropion of her right lower eyelid and notching of her right upper eyelid.

Case 6.—A 56-year-old woman had received radium treatments at 24 years of age for removal of excessive facial hair. She subsequently developed radiation dermatitis and facial scarring. She has had five basal cell cancers removed from her face. An insidious right-sided facial paralysis developed over a 3-year period. Because of increasing pain, a right-sided parotid mass, and the facial paralysis, a radical parotidectomy, temporal-bone excision, and neck dissection were performed. Extensive mutilation of the face and base of the skull resulted, without clearance of the margins.

Case 7.—A 60-year-old woman who had undergone multiple radiation treatments for facial acne as a child was referred to the senior author (W.R.P.). At the age of approximately 30 years, she first noted an ulcerated skin lesion of the left cheek. This lesion was diagnosed as basal cell carcinoma and was treated with a local curative excision. Since that time, she has undergone more than 30 excisions of facial carcinomas of both basal and squamous cell types. The last surgical procedure had been carried out 7 months before her referral to the University of Chicago (Ill). She had also undergone therapy with topical fluorouracil in an effort at chemoprophylaxis.

Her facial features were characteristic of a radiation-induced chronic radiodermatitis, with extensive scarring especially over the cheeks, upper lip, and nose. She had an obvious 0.5-cm lesion of the skin of the nasal tip, which was excised and found to be positive for basal cell carcinoma. The nasal tip was markedly deformed and partially missing because of prior excisions of skin cancers.

All malignant and premalignant local lesions were excised from the patient's face. Reconstruction was attempted only after a permanent-section pathologic diagnosis with evidence of clear surgical margins was obtained. Only those areas of the face that had been exposed to radiation and that demonstrated scarring, radiodermatitis, and/or prior skin cancer were removed.

In order to use cervical cutaneous tissues for facial reconstruction, we inserted four tissue expanders (250- and 400-mL size) under the midclavicular and supraclavicular skin of the neck. Prophylactic intravenous antibiotics were administered preoperatively. We injected 0.5% lidocaine with 1:100 000 solution of epinephrine into the skin and subdermal regions of the posterior neck hairline and of the supraclavicular areas. Subcutaneous pockets superficial to the platysma muscle were sharply developed for tissue expander insertion. The 250-mL oval expanders were used in the upper middle aspect of the neck, and the 400-mL oval expanders were used in the supraclavicular areas. Before placement of the expanders, hemostasis was achieved, and the pockets were copiously irrigated with sterile physiologic saline containing a cephalosporin antibiotic (1 g/100 mL). At the time of the insertion, the tissue expanders were partially (10% of maximum volume) filled with saline. The filler ports were positioned posteriorly in the scalp and upper aspect of the back.

Postoperatively the patient was given a 7-day course of antibiotics (erythromycin, 250 mg orally three times a day). Approximately 2 weeks later, the tissue expanders were injected weekly with 20 to 40 mL of saline. This procedure was carried out by the patient's local physician, who was admonished to monitor for infection, extrusion of the expanders, and tissue ischemia.

Two months after implantation of the tissue expanders, the patient was admitted for excision of her irradiated facial skin, removal of the tissue expanders, and facial resurfacing with bilateral cervical rotation advancement flaps consisting of the expanded tissue (Fig 2). The previously scarred, irradiated cheek, lip, and lower facial skin was excised and the cervical advancement flaps were rotated into the tissue defect. Advancement of the cervical rotation flaps produced tissue redundancy in the melolabial area (Fig 3). This tissue was used subsequently for nasal reconstruction. Three weeks later, a tubed, bipedicled flap was developed from the anterior redundant skin of the cervical advancement flap skin. The middle part of this flap was attached to the philtrum following full-thickness excision of the lip skin (Fig 4). After another 3 weeks, the proximal pedicles were cut and the tubes were unrolled and used for resurfacing of the nose. Three weeks after this procedure the lip-based pedicle was cut and used for reconstruction of the nasal ala. The columella was formed by advancement of the bony cartilaginous septum caudally and forward (Fig 5). A full-thickness skin graft was harvested from the medial upper aspect of the forearm and used for resurfacing of the entire upper lip (Fig 6). Thus, the cheeks, upper lip, and nose were reconstructed entirely with nonirradiated skin (Fig 7).

RESULTS

Patient 7 had tissue expanders inserted in October 1985. The final stage of her facial reconstruction, which included nasal resurfacing and placement of an upper lip full-thickness skin graft, was completed in March 1986. Since that time, the patient has had dermabrasion of her advancement-flap facial scars (Fig 8). She has been free of local disease, with no recurrence of skin cancer since the procedure was carried out. Before the resurfacing procedure, she had averaged two new or recurrent skin cancers a year for 5 years. Over a 25-year period, she had had 30 new or recurrent basal cell or squamous cell cancers in the previously irradiated field.

COMMENT

Modern radiotherapy with the use of supervoltage has eliminated, in large part, the once-common skin sequela of orthovoltage radiation, ie, chronic radiodermatitis. Orthovoltage radiation, which was used successfully in the past for treatment of acne, eczema, hirsutism, and other benign dermatoses, as well as tuberculosis and skin cancer, unfortunately has left a population of middle-aged and elderly patients suffering from its long-term, unremitting sequelae. Chronic radiodermatitis, facial scarring, and cancer are the major delayed effects of irradiating benign lesions and simple skin cancers.

Although the cosmetic consequences of chronic radiodermatitis of the face can have a significant emotional impact on the patient, it is the fear of cancer of the face, with the possibility of spread, that causes the greatest anxiety. The fear of facial disfigurement is shared by the patient and the surgeon.

Premalignant and malignant skin changes following irradiation may not appear for more than 25 years.[1] Early detection is crucial for prevention of both local and distant spread of the cancer. Therefore, the patient and the physician must constantly be vigilant. Early detection may be hampered by (1) the patient's fear of discovering facial cancer, that of possible facial disfigurement, and delay in seeking medical attention for early lesions; and (2) the likelihood that the entire irradiated skin will form multicentric lesions that can have the appearance of chronic radiodermatitis but may be malignant.[2]

The patient's and physician's concern about radiation-induced skin cancer is justified. Not only is there a propensity for multicentric lesions, but aggressive local growth can invade through embryonic fusion planes.[3] The incidence of cervical node metastases may be as high as 20% with squamous cell cancer of the integument.[4]

Skin cancer and premalignant

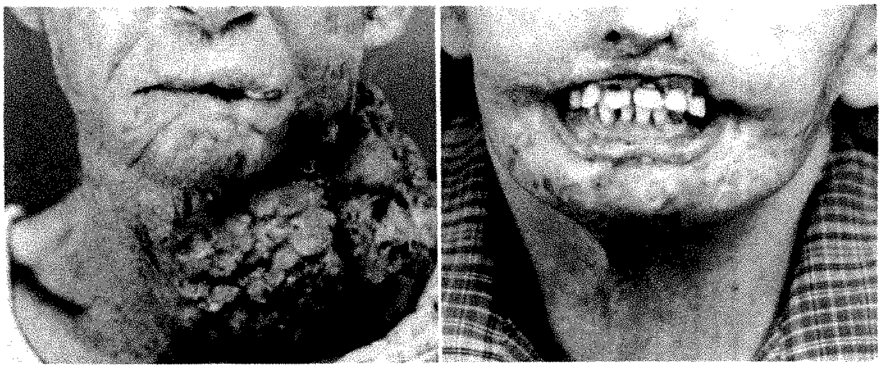


Fig 1.—Different patients who had received prior orthovoltage irradiation for benign dermatoses who subsequently developed multifocal and multiple recurrences for skin carcinoma.

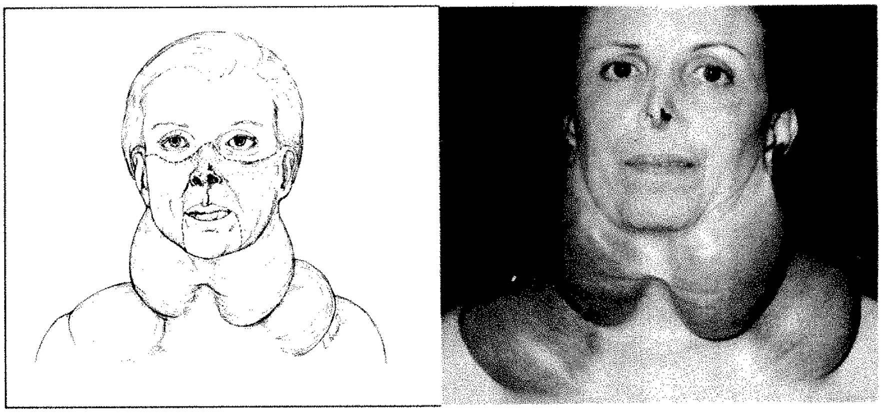


Fig 2.—Tissue expanders (250 mL and 400 mL) were placed in the middle aspect of the neck and supraclavicular areas 8 weeks prior to reconstruction. The stippled area indicates the area of skin to be excised.

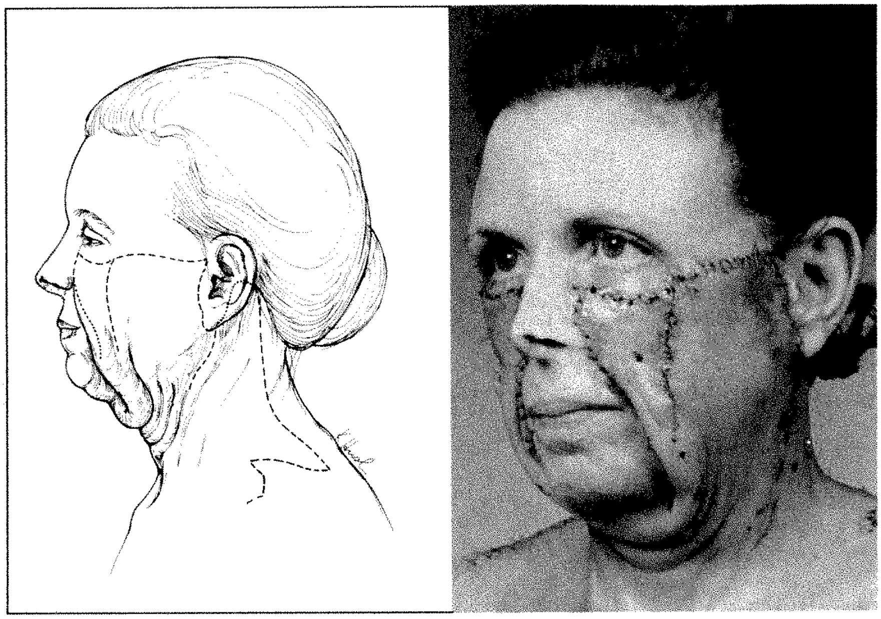


Fig 3.—Following advancement of the cervical rotation flaps. Note the anterior redundant skin beneath the chin.

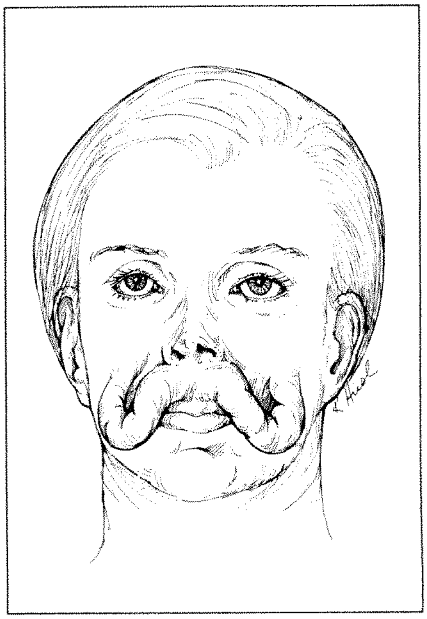


Fig 4.—The submental redundant skin was formed into a bipedicle flap with the central portion attached to the philtrum.

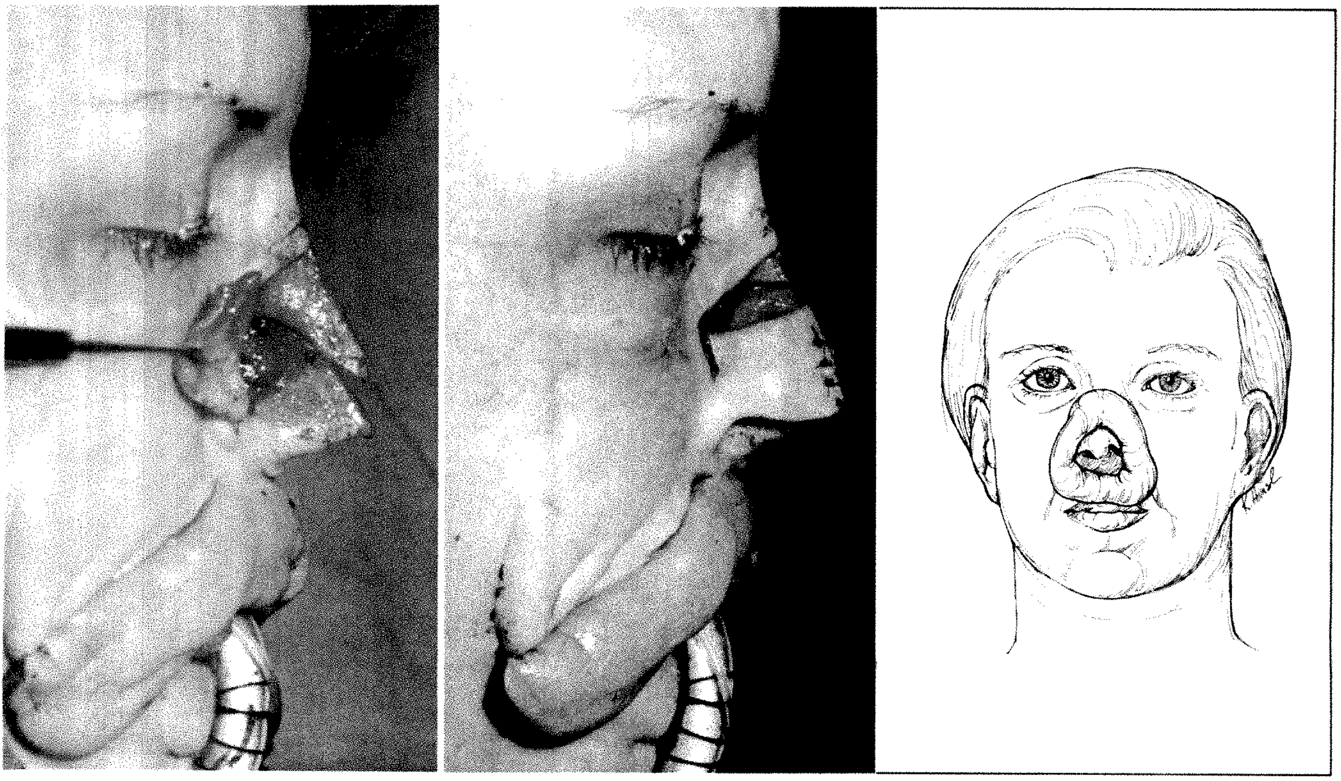


Fig 5.—Three weeks later, the nasal tip was reconstructed by advancing the septum. The pedicles were then transplanted to the upper dorsum. Left and center, The septum was advanced caudally to form the columella and support for the nasal tip. Right, The pedicles were transferred to the nose.

Fig 6.—Three weeks later the flap's philtrum base was detached from the lip to resurface the nasal tip. A full-thickness skin graft taken from the forearm was used to resurface the upper lip.

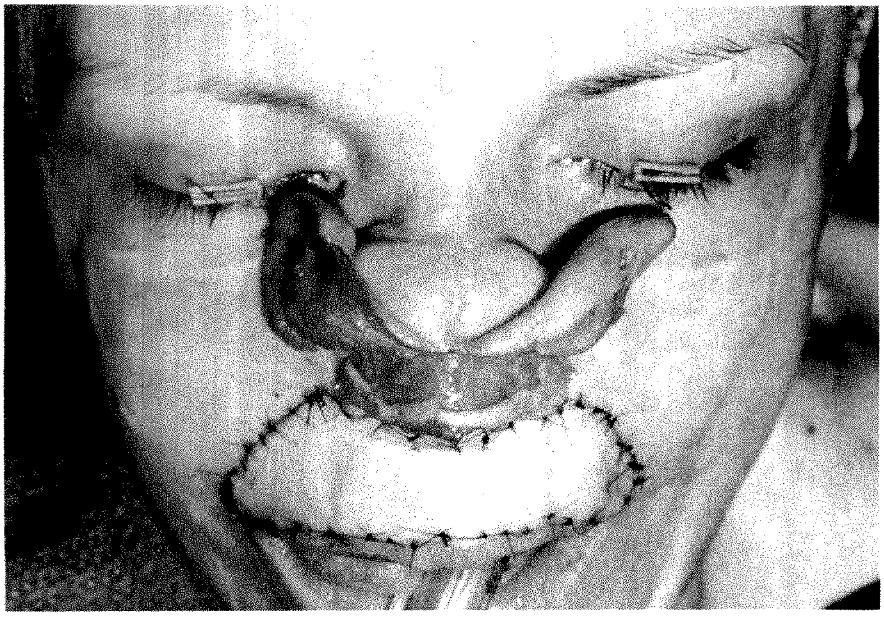
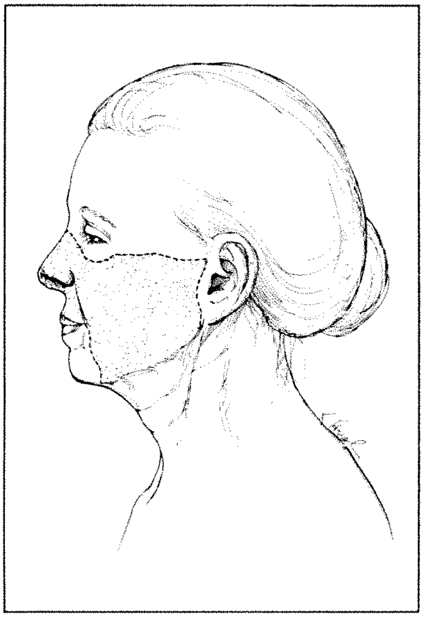


Fig 7.—Cutaneous area replaced with cervical rotation advancement flaps and full-thickness skin graft.



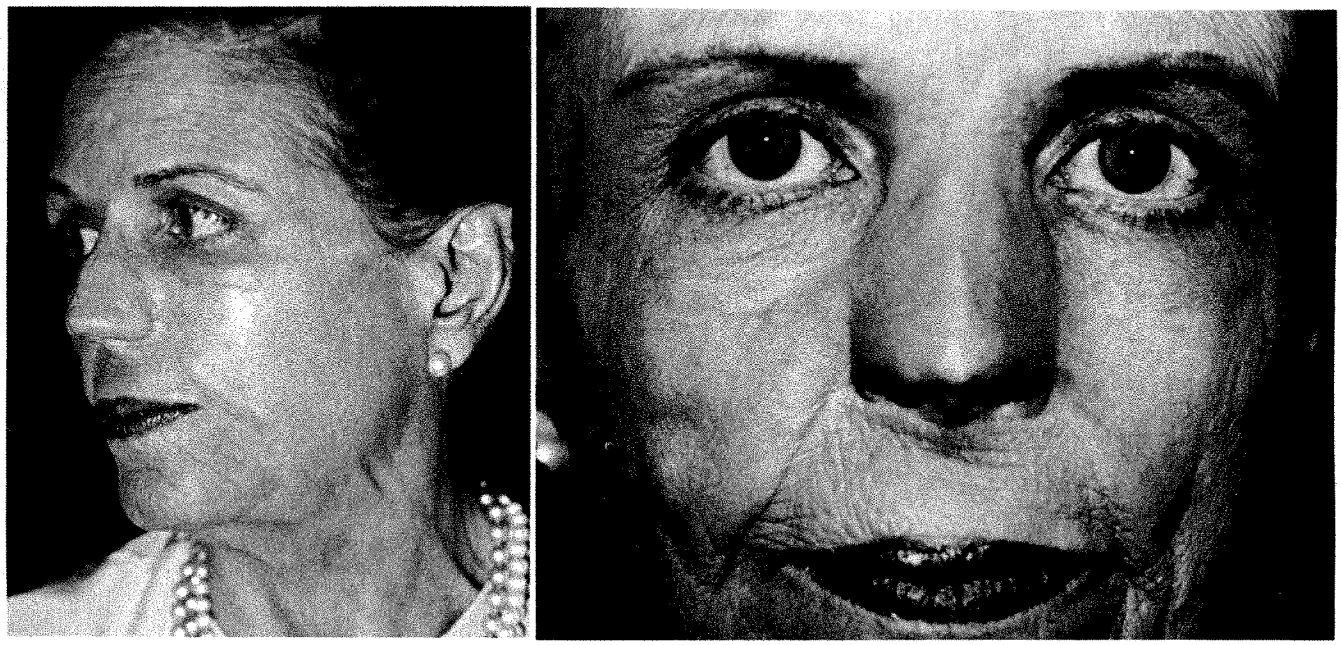


Fig 8.—Appearance 1 year later. Note flap's excellent color and texture matching the remaining facial skin.

changes can be treated successfully with topical chemotherapy, cryotherapy, or radiation therapy, or by local excision with or without the use of chemosurgical techniques.

Skin grafts and regional flaps have been used successfully for replacement of entire facial aesthetic units that have been damaged by radiation therapy.[5]

Full-thickness skin grafts have been used in resurfacing smaller facial units, ie, the nose, with good results. However, covering a larger surface area such as the middle aspect of the face with full-thickness skin grafts produces a significant donor site deformity. Skin grafts are not good for reconstructing composite tissue deficiencies such as the nasal ala or columella. Prior to the development of tissue expanders most reconstructive techniques for resurfacing large facial areas were difficult to complete without prolonged hospitalization and donor site deformity. The cervical rotation advancement flap has been found to produce excellent cosmesis when resurfacing cheek defects. This neck flap has excellent color match and texture comparable with facial skin. However, if this flap is used without expansion a large incision and extensive undermining onto the chest is necessary. Even with these maneuvers the flap will only resurface the cheek area. In our report the middle aspect of the face and the nose are reconstructed. This is the first report of nasal reconstruction with the cervical rotation advancement flap.

Our review of seven patients who had undergone radiation therapy some years previously for a benign skin condition demonstrated multiple recurrences of cancerous lesions within the previously irradiated fields, as well as metastases and death. We regard this as being secondary to late detection and undertreatment of recurrent skin cancers in the "condemned skin."

We propose that excision of the entire irradiated facial skin, regardless of whether or not cancer is present at the time, be performed for patients who have shown a propensity for multicentric, recurrent skin cancers. The face should then be reconstructed with nonirradiated skin grafts or flaps. Expanded neck skin provides sufficient tissue for rotation and advancement flap reconstruction of the middle aspect of the face and the nose. Excellent cosmesis, including a match of color and texture, is achieved with a local cutaneous flap.

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Extracranial Primitive Neuroectodermal Tumor of the Head and Neck

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• Malignant peripheral neuroectodermal tumors are rare neoplasms of the head and neck. We describe a case of a teenage girl presenting with this neoplasm in the head and neck. The clinical histological and ultrastructural features are reviewed and presented, along with guidelines for the management of this highly aggressive neoplasm.

***(Arch Otolaryngol Head Neck Surg.* 1990;116:475-478)**

Peripheral primitive neuroectodermal tumors (PNETs) are unusual neoplasms rarely presenting in the head and neck. In soft tissue these tumors arise from the nonautonomic nervous system and display neuronal differentiation.[1-3] They share certain features and characteristics with classic neuroblastoma and with some central nervous system tumors.

Although there is some uncertainty regarding the natural history of these tumors, with relatively few cases reported in the literature, the results of treatment have been rather unfavorable. Since these tumors are rarely encountered by and relatively unfamiliar to the head and neck surgeon, we describe the case of a patient presenting with a primary head and neck manifestation of this tumor. Subsequently, the pathology, clinical features, and treatment of these tumors are reviewed and described.

REPORT OF A CASE

A previously healthy 15-year-old white female patient was referred to the Otolaryngology–Head and Neck Surgery Department at the Montreal (Canada) Children's Hospital with a 4-month history of a lump above the right zygomatic arch area (Figs 1 and 2). This lump had steadily increased in size and she had previously been examined at another institution where needle aspiration of this lump had been attempted unsuccessfully.

The patient denied a history of trauma, visual disturbance, or pain. She was essentially asymptomatic, but apprehensive and concerned about the alteration in her appearance. Physical examination revealed an otherwise well 15-year-old girl with a 4 × 6-cm soft, noncystic fixed lump in the right temporal area, just above the zygomatic arch (Figs 1 and 2). There were no other subcutaneous lumps and no palpable cervical or axillary adenopathy. There were no cranial nerve deficits.

Roentgenographic investigations including facial bone and sinus roentgenograms, ultrasonography, chest roentgenograms, and high resolution contrast-enhanced computed tomography were performed. They revealed an extracranial and extraorbital soft-tissue mass in the right temporal area (Fig 2). There was bony erosion of a still intact right lateral orbital wall. The mass was believed to be under the temporalis muscle, although this could not be clearly distinguished from the mass itself. Also, clouding of the right maxillary antrum was present.

Since management of this lump would be dictated by the tissue diagnosis, a diagnostic incisional biopsy of this lump was performed as an outpatient procedure. A diagnosis of malignant PNET was made. Further investigations performed included ultrasonogram of the abdomen, high resolution computed tomography of the chest and abdomen, urinary and serum catecholamine levels, and testing for multiple endocrine neoplasia. The results of these tests were normal.

Consideration was given to performing a total maxillectomy and exploration of the infratemporal fossa. In view of the apparently poor prognosis for these tumors despite aggressive combined modality treatment, the patient and her family agreed only to local resection of the tumor without maxillectomy followed by radiation and chemotherapy.

The surgical approach to this tumor was a hemicoronal incision extended inferiorly in the preauricular area. The temporal mass was removed with the temporalis

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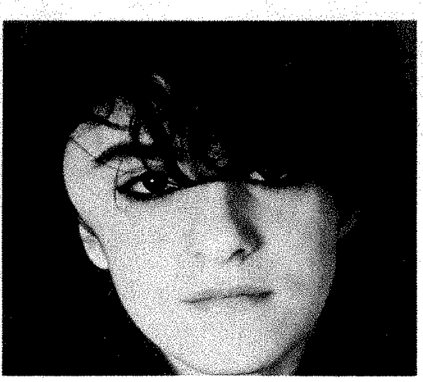

Fig 1.—Preoperative appearance of patient with a right temporal mass.

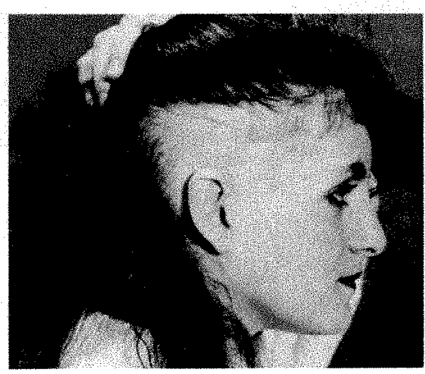

Fig 3.—Postoperative appearance of patient 39 months after combined treatment with surgery, radiation, and chemotherapy. Note some residual alopecia of temporal scalp that can be camouflaged.

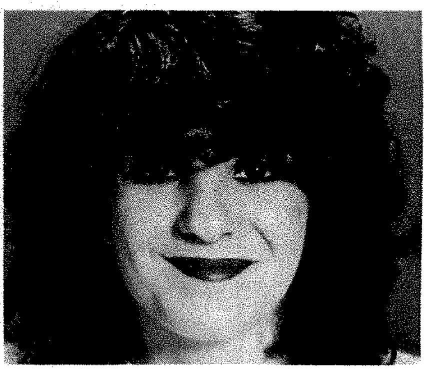

Fig 4.—Same patient as in Fig 3. Note that some residual alopecia of the temporal scalp that can be camouflaged with a hair piece.

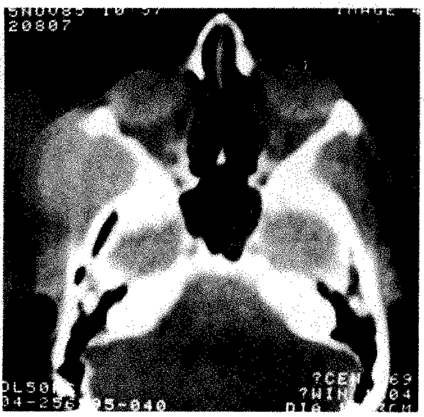

Fig 2.—Preoperative axial computed tomography showing a right temporal mass indistinguishable from the temporalis muscle.

muscle and with stripping of an adjacent cuff of pericranium to obtain a cuff of normal tissue. The site and tract of the previous biopsy was also widely excised. Intranasal antrostomy and curettage of the right maxillary antrum mucosa revealed no evidence of tumor on histologic examination. Unfortunately, the tumor also extended into the infratemporal fossa where gross tumor was removed, but without adequate margins. No cranial nerves were sacrificed.

Postoperatively she received chemotherapy with vincristine, 2.0 mg/m^2 (body surface area), doxorubicin (Adriamycin), 45 mg/m^2, and cyclophosphamide, 600 mg/m^2; this was given over six cycles. She also received 5400 Gy of external beam radiation over 6 weeks.

The patient is currently alive and well, free of disease 3 years after treatment (Figs 3 and 4). She continues to be followed up closely. Three months postoperatively, baseline computed tomography and magnetic resonance imaging were performed followed by serial scans every 6 months. These continue to show no evidence of recurrence or further erosion of the lateral orbital wall.

HISTOPATHOLOGICAL FINDINGS

The excised specimen measured 4 × 3 × 1 cm, and consisted of fibromuscular tissue diffusely infiltrated by a soft, somewhat gelatinous, pinkish-white tumor. Microscopically, the tumor showed no specific architectural pattern, and was composed of small primitive cells with scanty cytoplasm, round or oval nuclei with evenly dispersed chromatin, and inconspicuous nucleoli. Mitoses were frequent and tumor necrosis was fairly prevalent (Fig 5). No definite rosettes or pseudorosettes could be identified. Vascular invasion was present and the tumor extended to the surgical margins of resection.

With special stains and immunohistochemistry, there was periodic acid–Schiff positive staining in some cells. Neuron-specific enolase was focally positive. Ultrastructural examination revealed a population of cohesive, round to ovoid cells, with frequent interdigitating dendritic processes united by junctional complexes (Figs 6 and 7). The cytoplasm contained abundant ribosomes, paranuclear Golgi apparati, a few strands of rough endoplasmic reticulum, and a moderate number of round to ovoid mitochondria (Fig 7). Occasional elongated cell processes contained microtubules and small, dense neurosecretory type granules measuring 80 to 120 nm in diameter (Fig 7). Nuclei were frequently notched with discrete margination of chromatin and small nucleoli.

COMMENT

Malignant PNETs of peripheral origin are relatively uncommon, with some confusion surrounding their histopathological diagnosis and classification. Recent developments have resulted in better characterization and recognition of this tumor as a distinct entity among other small, round cell tumors such as rhabdomyosarcoma, lymphoma, Ewing's sarcoma, and classic neuroblastoma.

The category of PNETs[4,5] includes central neuroectodermal tumors that involve the brain and spinal cord, and peripheral neuroectodermal tumors. This group of peripheral neuroectodermal tumors includes the classic neuroblastoma found in childhood and other peripheral neuroepitheliomas (also referred to as peripheral neuroblastoma) that involve soft tissue and bone.[4,5] By definition, a peripheral neuroepithelioma is a PNET arising from peripheral, nonautonomic neuronal tissue. Peripheral neuroepitheliomas are not usually associated with elevated serum catecholamine levels. Embryologically, these tumors are considered to have originated from the neural crest. This can be supported by immunohistochemical methods.[6]

Classic neuroblastoma generally occurs in children less than 5 years of age, while PNET tends to occur in older children and young adults. Peak

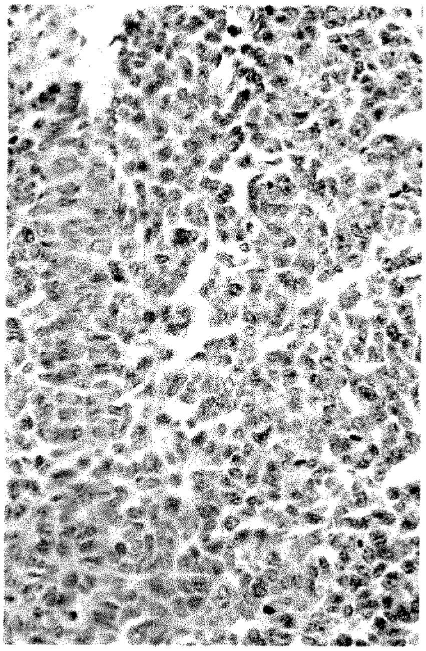

Fig 5.—Light microscopy shows patternless growth of primitive cells. Note the high frequency of mitotic cells (×250).

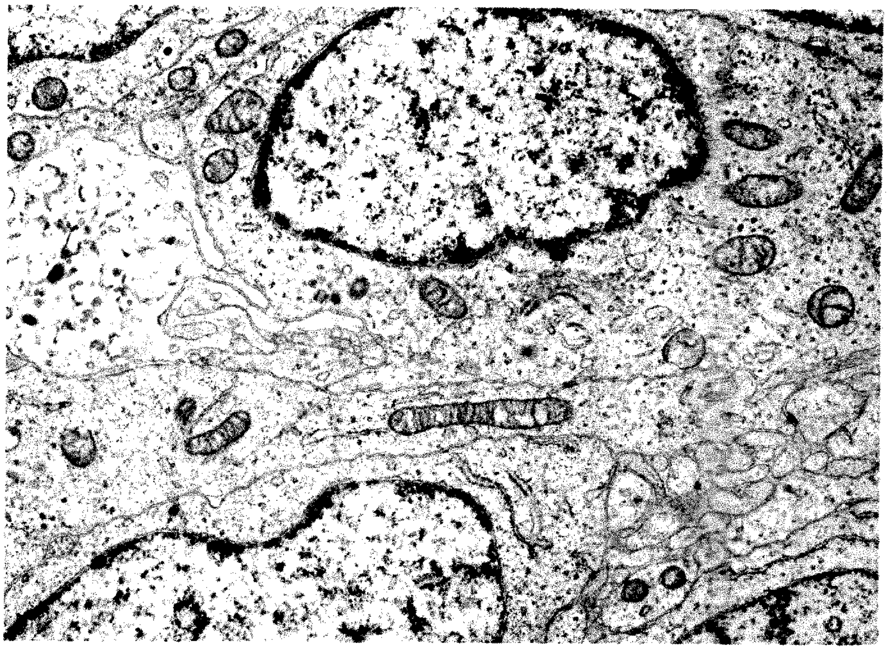

Fig 6.—Ultrastructurally, the cells are united by junctional complexes and the presence of interdigitating processes (right lower area) (uranyl acetate-lead citrate, ×12 000).

incidence in a series of 42 patients was in the adolescent years, while reviews of the reported cases found that 75% occurred before age 35 years.[4,6] Despite these clinical differences, PNET resemble classic neuroblastoma by light microscopy, electron microscopy, and even immunohistochemistry. This may pose a diagnostic dilemma: how to distinguish peripheral PNET from a metastatic neuroblastoma? Enzinger and Weiss[4] suggest that the diagnosis of peripheral PNET can only be made by exclusion, following an extensive search for a primary neuroblastoma.

Recent developments suggest a link between Ewing's sarcoma and peripheral PNET on the basis of an identical chromosomal reciprocal translocation demonstrated to exist in both.[4,6,7] This translocation is absent in classic neuroblastoma that is associated with its own different set of chromosomal anomalies.[5] Light microscopy may not differentiate Ewing's sarcoma from PNET, but ultrastructural observation of neurosecretory granules, interdigitating cell processes, and microtubules will distinguish PNET.[6,8] Also, in Ewing's sarcoma the cytoplasm is usually rich in glycogen.

The ultrastructural findings in our case are typical of previously described findings in PNET, namely the presence of junctional complexes and confluent cell processes containing occasional neurosecretory type granules, microtubules, and intermediate filaments.[8,9] Malignant lymphoma characteristically lacks junctional complexes. Granules are absent in alveolar rhabdomyosarcoma that would otherwise contain glycogen and myofilaments, depending on the degree of differentiation. Small-cell carcinoma or Merkel's cell carcinoma is unlikely to be encountered in the pediatric age group, and are likely to be ultrastructurally

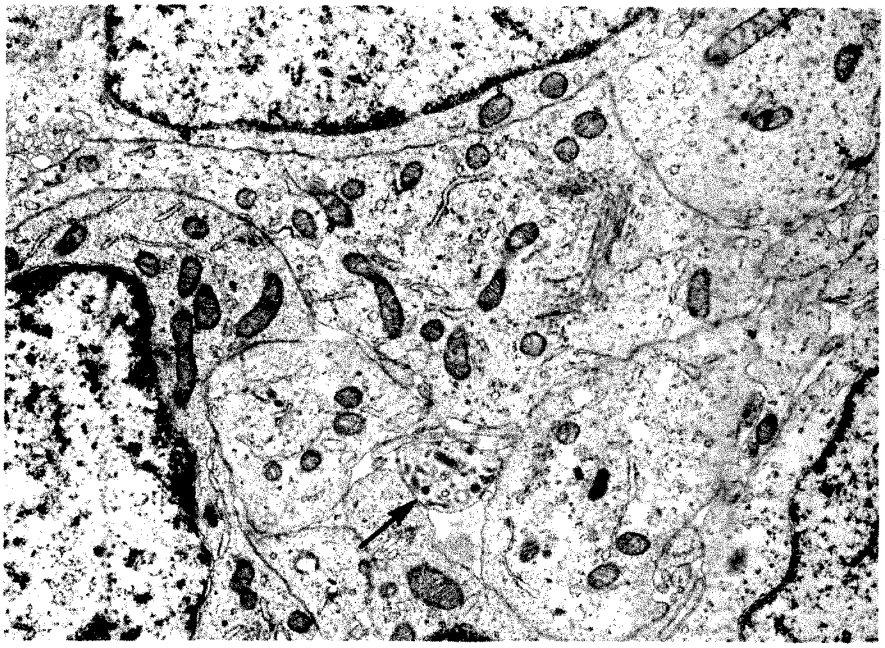

Fig 7.—Ultrastructurally, rare membrane-bound neurosecretory-type granules (arrow) are present in a cell process. The cytoplasm also displays a Golgi apparatus and short strands of rough endoplasmic reticulum (uranyl acetate-lead citrate, ×12 000).

characterized by less elaborate cell processes, more prominent desmosomal type junctional complexes, paranuclear intermediate filaments, and even tonofibrils.

Although the diagnosis of malignant PNET is becoming more frequent as a result of improved pathologic diagnostic methods and criteria, it remains relatively rare, with only a handful of cases involving the head and neck.[6,7,10] Jurgens et al[6] reviewed 42 cases of malignant peripheral PNET and found only 4 cases involving the head and neck. The most frequent location of a malignant peripheral PNET was the chest wall, 57% in Jurgens and coworkers' series, and this is in agreement with the findings of other investigators.[1,2,4,6-8] Interestingly, in 38% of Jurgens and coworkers' cases,[6] the initial histological diagnosis was Ewing's sarcoma.

Since malignant peripheral PNET is unlikely to present with a primary site in the head and neck, an extensive workup to rule out the possibility of a metastatic neuroblastoma should be performed. The tumor may sometimes be associated with a peripheral nerve.[6]

Primitive neuroectodermal tumor is considered to be a highly aggressive malignant neoplasm with a propensity for rapid distant metastases to lung, liver, and bone.[4,6-8] Treatment with combined therapy including surgery, radiation, and chemotherapy is advocated.[1,3,6-8,11,12] The results of treatment for malignant peripheral PNET in the small number of patients reported have been poor. Jurgens et al[6] found a 56% disease-free 3-year survival in 32 patients with localized disease without metastases. They also reported a marked tendency toward local recurrence when surgical resection was marginal or limited, and therefore advocated wide surgical resection followed by radiation and chemotherapy.

External beam radiation therapy using 50 to 65 Gy to the primary site and regional nodes is advocated.[1,3,6-10] Chemotherapeutic regimens similar to those used for Ewing's sarcoma and neuroblastoma are currently being used in the treatment of these patients.[1,3,6,8,11]

Doxorubicin (45 mg/m^2), vincristine (2 mg/m^2), and cyclophosphamide (600 mg/m^2) are the agents most commonly being used in these regimens.[1,3,6,8,9]

Malignant peripheral PNET rarely presents with a primary in the head and neck; therefore the diagnosis requires exclusion of a metastatic neuroblastoma. Treatment using wide surgical resection of the primary site followed by external beam radiation using 50 to 65 Gy and chemotherapy appear to offer the best results. While complete remissions following treatment are common, long-term disease-free survival has been less encouraging. Careful long-term follow-up of these young patients is essential.

We thank M. J. Black, MD, and R. C. Lachance, MD.

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Subglottic Cysts in the Premature Infant

James D. Smith, MD; Robin Cotton, MD; Charles M. Meyer III, MD

• **Supraglottic cysts in the newborn are a well-recognized entity, but subglottic cysts have been rarely reported. Over the past 6 years we have observed subglottic cysts in nine patients with relatively long intubations from the neonatal intensive care unit of two university hospitals. Most frequently the patients were extubated and did well for weeks or months, but then they had progressive biphasic stridor. On endoscopy the patients had a subglottic stenosis that was irregular but with a smooth mucosal lining. Usually the cysts were apparent, but in two patients the mucosa was thickened and the patients were treated as a subglottic stenosis with tracheostomy. These subglottic cysts were recognized at the time of laryngotracheoplasty. In six patients the cysts were managed either by marsupialization with cup forceps, endoscopic diathermy, or carbon dioxide laser without recurrence. It is our belief that this condition is most likely due to scarring and obstruction of mucus glands of the subglottic area from prolonged intubation. This entity should be recognized and looked for in the neonate who has an acquired subglottic stenosis and should first be treated conservatively with endoscopic marsupialization.**

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Although supraglottic cysts and laryngoceles are frequently recognized, subglottic cysts have been rarely reported.[1-6,8] Over the past 6 years, in two separate neonatal intensive care units, we have had nine cases of subglottic mucus retention cysts in premature infants who had been intubated for varying lengths of time.

REPORT OF CASES

The following cases of subglottic cysts have been diagnosed at the Children's Hospital Medical Center, Cincinnati, Ohio, and the Oregon Health Sciences University, Portland, from 1982 to 1988.

Case 1.—This 22-month-old black male infant was born prematurely and intubated for 1 month in the neonatal period for respiratory distress syndrome. His history was significant for transient reactive airway disease and pneumonia. The child presented with cough, stridor, and increasing respiratory distress at 8 months of age at which time microlaryngoscopy and bronchoscopy revealed a 75% subglottic compromise from cystic lesions in the posterior and right lateral subglottis. These cysts were subsequently removed endoscopically, and follow-up with microlaryngoscopy and bronchoscopy 1 month later revealed a normal subglottis. This child has had no stridor or upper airway compromise since.

Case 2.—This 3½-year-old girl was born prematurely and intubated at birth for 4 hours for suspected respiratory distress syndrome, which was later not confirmed, and the child was extubated. On the 14th day of life she was reintubated for a period of 4 days because of increasingly prolonged apnea spells. Following this, she was treated medically for necrotizing enterocolitis, which prolonged her hospitalization to a total of 2 months from the time of birth.

Shortly after being discharged the child developed stridor and increasing respiratory distress, for which she underwent bronchoscopy and was found to have severe subglottic stenosis; a tracheotomy was performed. Subsequently, her airway was well maintained with a tracheotomy, and she was referred from Minneapolis, Minn, to Cincinnati, where laryngoscopy and bronchoscopy showed an irregular mucosal-covered soft subglottic stenosis. A laryngotracheoplasty was then performed with anterior costal cartilage graft. At the time of surgery submucosal cysts were found to be present in addition to the stenosis, and these were removed. The stenosis was found to be mainly left lateral but was also posterior and right lateral. The child had an uncomplicated postoperative course, with early removal of the stent and early decannulation.

On follow-up with microlaryngoscopy and bronchoscopy she was found to have a good result with an adequate subglottic lumen and a viable anterior graft in position.

Case 3.—This 16-month-old white boy was a premature infant who required a ventilator for the first 10 days of life for respiratory distress syndrome. He then required supplemental oxygen for a period of 4 months and developed bronchopulmonary dysplasia requiring use of furosemide (Lasix), spironolactone (Aldactone), and theophylline (Theo-Dur). He then had an episode of suspected croup, with respiratory distress and cyanosis requiring 3 days of intubation at 4½ months of age. Following this episode, he had continuing stridor and he underwent a microlaryngoscopy and bronchoscopy at 9 months of age that revealed a large left subglottic cyst. This cyst was removed with diathermy using an endoscopic approach, and 1 week later the laser was used endoscopically for removal of the remaining small left posterior and anterior cysts. Since that time the patient has done well and has not had stridor or recurrent cyanosis.

Case 4.—This 2-year-old white boy was born prematurely and intubated for 10 weeks in the neonatal period for respiratory distress syndrome. His history was significant for patent ductus arteriosus ligation. The child presented at 20 months of age with frequent episodes of respiratory distress and two episodes of cyanosis. Microlaryngoscopy and bronchoscopy revealed subglottic cysts on the anterior and posterior walls. These were removed in three endoscopic procedures. Since then the patient has been well and has had no recurrence of respiratory distress or cyanotic spells.

Case 5.—This male infant was born at 29 weeks' gestation and weighed 1170 g. He had immediate respiratory problems necessitating intubation for 5 days. There were two subsequent intubations for 2 and 6 days each. There were mild retractions and chronic bronchopulmonary dysplasia, but the child was discharged at 2 months of age.

Two months after discharge the child was readmitted with bronchitis, tachypnea, wheezing, and retractions. There was biphasic stridor, but this improved and he was discharged 3 days later. The wheezing persisted and the child was readmitted at age 5 months with increasing biphasic stridor and retractions. Direct laryngoscopy and bronchoscopy revealed a circumferen-

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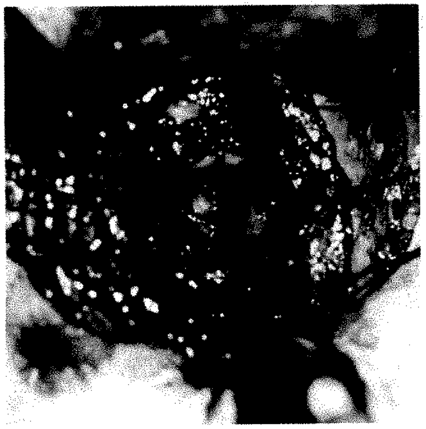

Fig 1.—Subglottic area at laryngotracheoplasty with cyst in situ.

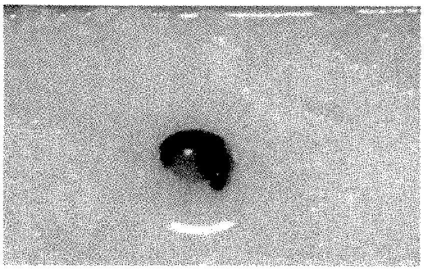

Fig 2.—Removed subglottic cyst.

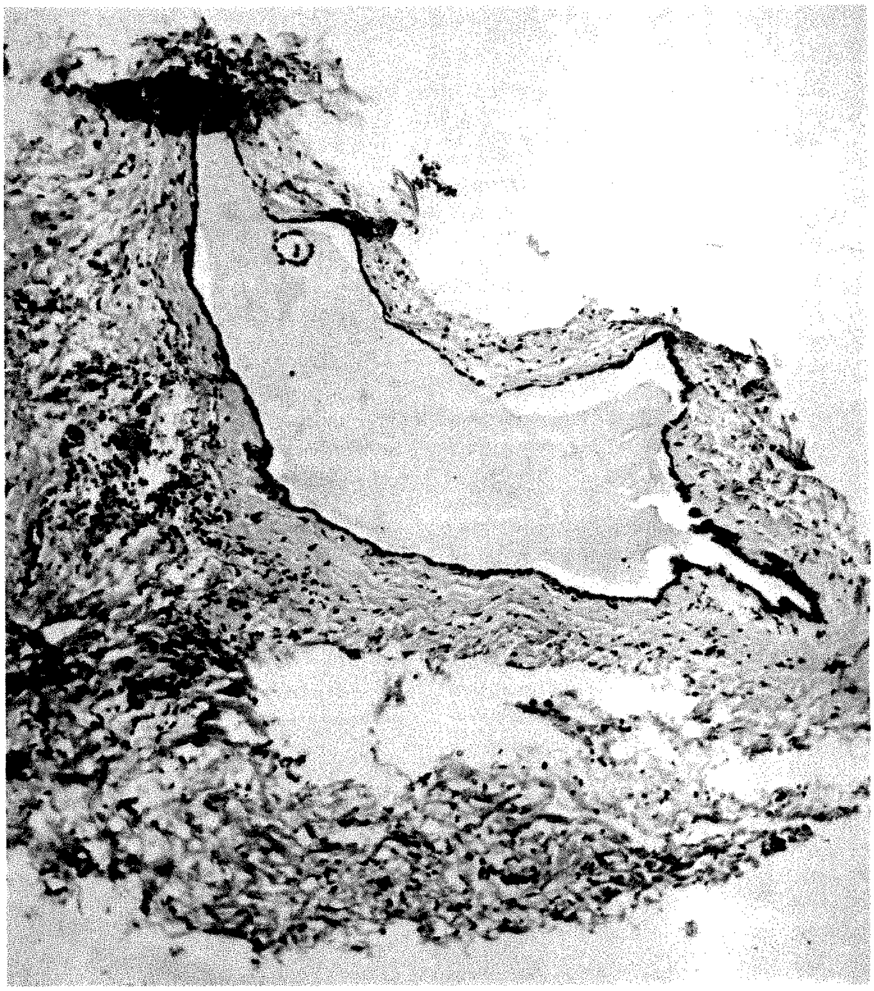

Fig 3.—Photomicrograph of subglottic cyst with cuboidal epithelial lining and surrounding fibrous tissue (magnification ×100).

tial soft subglottic stenosis that was easily dilated with a 3-mm bronchoscope.

At age 6 months the biphasic stridor had returned and the patient underwent repeated bronchoscopy and dilatation with a 3.5-mm bronchoscope. At age 8 months, symptoms recurred and again bronchoscopy revealed the soft stenosis that was dilated with a 3.5-mm bronchoscope, but the collapsing tissue necessitated a tracheotomy. The child continued to have persistent pulmonary problems.

Repeated bronchoscopies were performed at 6-month intervals without improvement of the stenosis. At age 26 months, an Evans-type castellating laryngotracheoplasty with an Aboulker stent was performed. At the time of surgery a bronchoscopy revealed three mounded areas in the subglottic area. On opening the subglottic area the cricoid appeared normal, but deep below the mucosa were three small inclusion cysts containing clear fluid (Figs 1 through 3). The stent was left in place for 2 months, and 3 months later the patient was successfully decannulated. One year later he had had no further upper airway problems or stridor.

Case 6.—This male infant was 27 weeks gestational age, weighed 950 g, and was intubated shortly after birth with a 2.5-mm endotracheal tube. At 8 days of age a patent ductus arteriosus was ligated. He developed *Candida* colonization of the lungs, but was extubated at 20 days of age. He was hospitalized for a total of 75 days with long-term carbon dioxide retention and bronchopulmonary dysplasia.

One month after discharge he had increasing respiratory distress associated with an upper respiratory tract infection. He was admitted, improved rapidly, and discharged 6 days later.

Four days after discharge he was readmitted with inspiratory stridor. On flexible nasopharyngoscopy a subglottic mass was noted. At bronchoscopy three subglottic cysts were identified and marsupialized with the carbon dioxide laser. There was no recurrence after 6 months.

Case 7.—This infant was born at 29 weeks' gestational age, weighed 950 g, and was intubated 2 hours after delivery, and he remained intubated for 3 weeks. After extubation the child had chronic problems with carbon dioxide retention, tachypnea, and required 40% oxygen. At age 3 months discharge was imminent, but the child began to have "funny breathing" with feedings. Pulmonary consultation was obtained and the patient was noted to have inspiratory and expiratory stridor. Flexible nasopharyngoscopy was performed and a subglottic mass was noted.

At bronchoscopy there was a thickened mass on the left lateral subglottic wall that was removed with the laser. The patient was intubated for 24 hours, then was extubated, and did well. Three years later there was no evidence of recurrence.

Case 8.—This premature female infant was born at 27 weeks' gestation and weighed 900 g. She was intubated for 5 days for respiratory distress syndrome, but was then extubated and initially did well. She had progressive symptoms of stridor at about 8 months of age and, on endoscopy, was noted to have subglottic cysts. These were removed with diathermy at two separate procedures 1 week apart. She had no evidence of recurrence after 2 years.

Case 9.—This premature female infant was born at 30 weeks' gestation and weighed 1000 g. She was intubated for 90 days, but had multiple complications including severe bronchopulmonary dysplasia. At 1 year of age a diagnosis of severe subglottic stenosis and subglottic cysts was made. She had multiple endoscopic procedures, but because of the severity of the subglottic stenosis a tracheotomy was performed. A laryngotracheoplasty was planned but she died of bronchopulmonary dysplasia complicated by a respiratory syncytial virus infection.

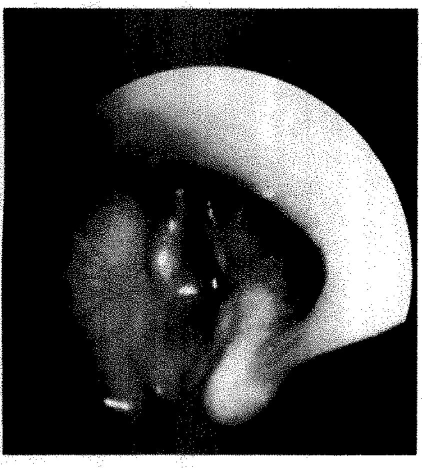

Fig 4.—Endoscopic view of subglottic cyst.

TREATMENT

All patients with biphasic stridor and/or breathing difficulties need examination of the airway. An initial examination may be performed with flexible nasopharyngoscopy as described by Fan.[5] If no pathologic conditions are found to explain the symptoms, or if the examination is suboptimal, examination of the entire laryngotracheobronchial tree should be performed with the patient under general anesthesia using fiberoptic telescopic equipment. If at this examination there are pathologic findings in the subglottic area, a distinction between a subglottic stenosis and subglottic cysts should be made. A subglottic stenosis will usually be circumferential, is firm, and may not be amenable to bronchoscopic dilatation. Subglottic cysts will either be obvious or present with intact mucosa, with one or more soft mounds coming from the subglottic walls immediately below the vocal cords (Fig 4). Usually the bronchoscope may be passed through the obstruction with relative ease. If the cyst is thin walled it may actually rupture with this maneuver and provide the definitive treatment. If not, the cyst may be marsupialized using a cup forceps, endoscopic diathermy, or the carbon dioxide laser if it is available. We would give intraoperative steroids and observe the patient in the pediatric intensive care unit postoperatively. If the patient does well and it is believed that all the cysts were removed, follow-up with endoscopy would be repeated in 4 to 6 weeks.

COMMENT

Over the past 5 years we have independently recognized an entity of subglottic cysts in patients who were born prematurely, intubated for varying lengths of time, and then developed symptoms of subglottic stenosis several weeks to months later. In most cases the diagnosis of subglottic cysts was apparent at endoscopy, but in two patients a diagnosis of subglottic stenosis was made, a tracheotomy was done for an airway, and the cysts were recognized at the time of laryngotracheoplasty. In both of these patients the cysts were deep in the submucosa and appeared as a soft collapsing subglottic stenosis. The borders were rounded with intact mucosa rather than a tight circumferential stenosis. In retrospect, a patient born prematurely with a history of intubation and delayed onset of subglottic stenosis should be carefully examined for possible subglottic cysts. In those patients with obvious subglottic cysts, marsupialization with a cup forceps, diathermy, or carbon dioxide laser provided satisfactory treatment without recur-

Case Report Summary*

Case	Gestational Age, wk	Birth Weight, g	Intubation Length, d	Times Intubated	From Extubation to Diagnosis, mo	Treatment	Outcome
1	34	1400	30	1	7	Endoscopic removal	No recurrence over 14 mo
2	26	1000	4, 4	2	1½	Tracheotomy for subglottic stenosis, 3-mo-old; at age 3 y an LTP was performed with the finding submucosal cysts	Adequate lumen after LTP and anterior cartilage graft
3	26	1090	10, 3	2	8	Endoscopic diathermy followed in 1 wk with laser removal of remaining cysts	No recurrence over 8 mo
4	30	1100	70	1	18	Endoscopic removal in 3 procedures	No recurrence over 6 mo
5	29	1170	5, 2, and 6	3	4	Tracheotomy, 7-mo-old; LTP at 26 mo	No recurrence 1 y
6	29	950	21	1	2½	Endoscopic carbon dioxide laser removal	No recurrence 2½ y
7	27	950	20	1	2½	Endoscopic carbon dioxide laser marsupialization	No recurrence 1 y
8	27	900	5	1	8	Endoscopic diathermy with 2 procedures 1 wk apart	No recurrence after 2 y
9	30	1000	90	1	9	Several endoscopic procedures, severe subglottic stenosis, tracheotomy	Expired from BPD complicated by a respiratory syncytial virus infection, LTP was planned

*BPD indicates bronchopulmonary dysplasia; LTP, laryngotracheoplasty.

rence in six of our cases, although some required more than one procedure to remove all the cysts (Table). The two patients who had a laryngotracheoplasty also had satisfactory airways without recurrence of the cysts. One patient died of lung complications not associated with the subglottic cysts.

Subglottic lesions usually present with a history of biphasic stridor, cyanotic spells, recurrent apnea, and feeding problems. They may be due to congenital lesions such as subglottic hemangiomas or lymphangiomas, congenital subglottic stenosis, and postintubation subglottic stenosis.[4,7]

In 1968 Wigger and Tang[6] reported a premature infant intubated for 5 weeks who developed multiple complications and died at 3½ months of age. At autopsy a 5-mm subglottic mucus retention cyst was found to occlude 80% of the lumen. On microscopic examination there was intact mucosa, but surrounding scar tissue and microscopic mucus retention cysts were noted.

There were no further reports of similar findings until 1981 when Couriel and Phelan[2] presented three premature infants, all weighing less than 1000 g at birth, who had been intubated and who had delayed onset of subglottic narrowing diagnosed as subglottic cysts on direct laryngoscopy.[2] They made the point that subglottic narrowing in the immediate extubation period is secondary to mucosal edema and that delayed obstruction weeks to months later is usually due to scarring and subglottic stenosis. In two patients the subglottic cysts were relatively thin and easily ruptured with a bronchoscope without recurrence, but one had to be treated a second time with the carbon dioxide laser and a short intubation period.

Fan,[5] in presenting a technique for fiberoptic endoscopy in children, diagnosed a subglottic cyst in a 14-month-old infant who had been intubated in the neonatal period. This was removed surgically and no recurrence was reported.

Holinger et al[8] have presented 26 patients who had an anterior cricoid split for either primary or secondary subglottic stenosis. Three of these patients had subglottic cysts. One patient had a tracheotomy after failure of the anterior cricoid split. The stenosis was recognized, but the diagnosis of subglottic cysts was not made until the patient died of other causes and a postmortem examination was performed. There were multiple cysts and hyperplasia of the subglottic mucus glands on microscopic examination.

There are three other reports of subglottic cysts. Dagan et al[3] described a 2-month-old infant who presented with stridor and respiratory distress; she was intubated for 2 days, and then on direct laryngoscopy was found to have a subglottic mucocele. Chamberlain[1] reported a newborn with a subglottic cyst diagnosed shortly after birth. The patient had a tracheotomy, but died at 3 months of age. At autopsy there was a 1-cm cyst below the cords that was lined with pseudostratified ciliated columnar epithelium, but was covered with normal mucosa without inflammation or scarring, although there were some microscopic daughter cysts in the area. The third case was a 17-year-old girl presented by DeSanto et al,[4] in a review of 238 cysts of the larynx over a 20-year period. This was a bilobed cyst with the largest component (3 cm in diameter) externally and a 1-cm cyst internally in the subglottic area. It seemed to be similar to a fluid-filled laryngocele, but the components communicated directly through the thyroid cartilage that was believed to be in the area of a vascular channel.

From this review it would appear that there are rare congenital subglottic cysts,[1,3,4] but that there is a definite emerging entity of subglottic mucus retention cysts as a complication of intubation in premature infants.[2] We believe that the endotracheal tube produces erosion, inflammation, and then scarring in the subglottic area that results in sealing off the ducts of submucus glands and results in cyst formation. In several of our cases, as well as those reported in the literature, the cysts were multiple and there was microscopic evidence of scarring in the immediate area.[6]

With the expanding role of neonatology units and the increased survival rate in premature infants, this complication will no doubt be more frequently recognized. As otolaryngologists we are aware of the immediate problems from long-term intubation, such as subglottic mucosal edema, erosions, and granulations that can make extubation difficult.[9] Cotton and Seid,[10] as well as others, have used the anterior cricoid split procedure to prevent the need for tracheotomies in a high percentage of these patients.[8,11] The most commonly recognized delayed complication of long-term intubations has been cicatricial circumferential subglottic stenosis, which if symptomatic requires a tracheotomy and is usually treated definitively by some type of laryngotracheoplasty.[12] We must also be aware of the possibility that subglottic cysts may also be a delayed complication of intubation in the premature infant.

Although there have been isolated reports on this condition, it has not been widely recognized by otolaryngologists and neonatologists. We call attention to this entity so that it may be more widely recognized and treated appropriately with marsupialization of the cysts rather than being treated as a subglottic stenosis with tracheostomy.

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Vestibular Schwannoma Presenting With Sudden Facial Paralysis

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• Facial paralysis is an unusual manifestation of vestibular schwannoma, and generally signifies an advanced stage of tumor growth. We describe a case of eighth-nerve schwannoma that presented initially with rapid-onset complete unilateral facial paralysis. At the time of operation the nerve was found to be electrically intact despite marked compression by tumor. The facial nerve was preserved and facial motion has partially recovered postoperatively. All unexplained persistent facial paralysis should be evaluated by magnetic resonance imaging with paramagnetic contrast enhancement.

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Sir Terence Cawthorne[1] once stated "All that palsies is not Bell." While Bell's (idiopathic) facial palsy is the most common clinical entity of facial weakness, tumor is always in the differential diagnosis of a persistent facial paralysis. An estimated 5% of facial palsies are secondary to tumors.[2] These relatively uncommon cases of facial paralysis due to tumor are usually associated with either facial nerve neurilemoma, tumor contiguous with the facial nerve, or metastatic disease.[3,4] Facial paralysis can also occur in eighth-nerve schwannomas, where it is regarded as a late finding.[5] The following unusual case demonstrates rapid-onset facial paralysis as the initial manifestation of a relatively small vestibular nerve schwannoma.

REPORT OF A CASE

A 23-year-old white woman presented to her physician for treatment of right-sided facial paralysis. This had developed over the course of several hours, less than half a day. The initial diagnosis was Bell's palsy and she was treated with a trial of oral steroid therapy. The treatment had no beneficial effect on her facial paralysis. Two weeks later she developed right-sided hearing loss. There was no vertigo or dysequilibrium. The patient also denied tinnitus and any prior otologic problems. There were no facial paresthesias, but a flattening of taste sensation was noted. Three months after her symptoms developed she was referred to us for further evaluation and treatment.

Results of a physical examination revealed tympanic membranes of normal appearance and mobility. Tuning fork localized to the left side on the Weber test. No spontaneous nystagmus was observed. There was a complete right-sided facial paralysis, but no other focal neurologic findings. Audiogram showed profound sensorineural hearing loss on the right side. Hearing was normal on the left side. Acoustic reflexes were consistent with right-sided anakusis. An electronystagmogram showed mild spontaneous left-beating eyes-closed nystagmus. Severe vestibular hypofunction on the right side was evident on 20°C and ice-water caloric testing. Facial nerve electrodiagnostic tests were performed. Pontogram results were compatible with a right-sided peripheral facial nerve lesion. An electromyogram demonstrated fibrillation

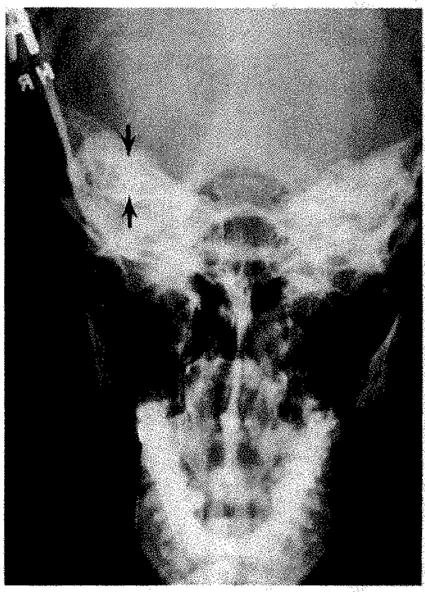

Fig 1.—Towne projection roentgenogram showing widened internal auditory canal on the right side (arrows).

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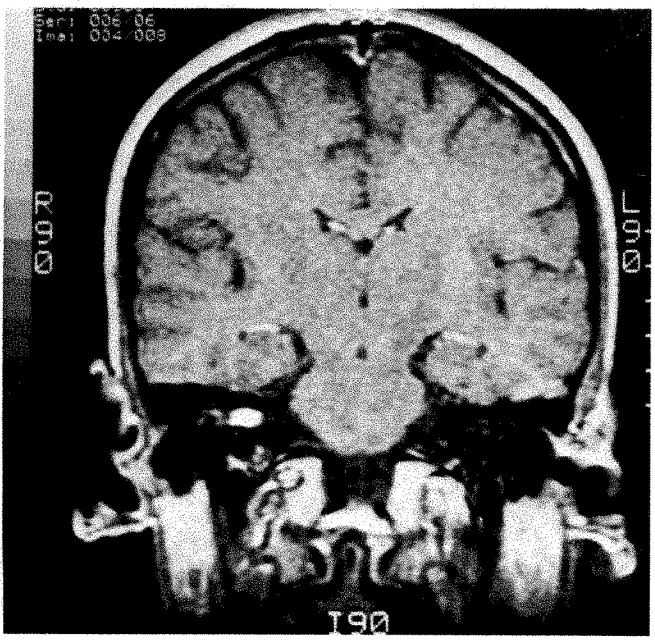

Fig 2.—T_1-weighted magnetic resonance imaging scan in the coronal plane showing gadolinium-enhanced lesion in the right internal auditory canal region.

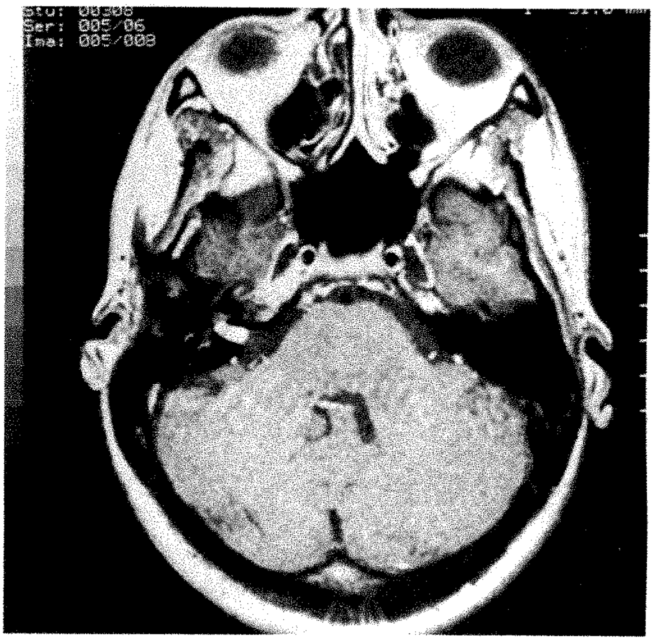

Fig 3.—Magnetic resonance imaging scan in the transverse plane showing gadolinium-enhancing right internal auditory canal mass.

potentials. Electroneurography showed no response (to maximal stimulation) on the right. A Towne projection roentgenogram demonstrated a widened internal auditory canal on the right side (Fig 1). Magnetic resonance imaging (MRI) with intravenous gadolinium contrast was obtained, and an enhancing intracanalicular lesion was clearly visualized on the right side (Figs 2 and 3).

A translabyrinthine surgical approach was undertaken for removal of the lesion. The main tumor mass originated in the superior vestibular nerve; in addition, noncontiguous tumor was present within the posterior semicircular canal. A portion of the intracanalicular segment of nerve VII was substantially thinned and had decreased perineural vascularity due to compression by the tumor. However, after excision of the lesion, stimulation of the facial nerve with 0.25-volt DC pulses distal to the geniculate ganglion and 0.5-volt pulses proximal to the compressed region produced facial movement. In the immediate postoperative period, facial movement was not present. However, 3 months postoperatively right-sided midfacial motion was partly recovered, including near complete eye closure and moderate orbicularis oris function. The diagnosis was schwannoma.

COMMENT

Vestibular nerve schwannoma is the most common mass lesion to occur in the cerebellopontine angle region. Although the true incidence of this lesion is not reliably known, any unexplained unilateral otologic symptoms must be regarded with suspicion for presence of an eighth-nerve tumor. Typically the tumors involve the vestibular nerve in the medial internal auditory canal, and they may extend out into the cerebellopontine angle or, less frequently, remain primarily intracanalicular.[6] Histologically, schwannoma is found 80% to 90% of the time. Meningioma and cholesteatoma are the next most common masses found in the cerebellopontine angle.[7]

Auditory symptoms, either unilateral sensorineural hearing loss or tinnitus, are by far the most common clinical presentations of a vestibular schwannoma. Vestibular dysfunction may be evident from complaints of vertigo or unsteadiness. As the tumor enlarges, other cranial nerve findings may appear, most notably sensory changes reflecting impingement on the trigeminal nerve.[8]

Curiously, facial paralysis is an uncommon manifestation of vestibular schwannoma. Neely and Neblett[9] reported preoperative facial paralysis in 6.1% of their review of 49 eighth-nerve schwannomas, and a rate of only 3.2% was noted in a series of 500 patients by Brow.[10] When facial paralysis occurs as a late finding, a large tumor is found, generally with other cranial nerve deficits, particularly involving nerves IX and X.[11] In contrast, the rare primary facial nerve neoplasms (neurilemomas) may present relatively early with facial weakness. Progressive facial weakness or, less commonly, sudden facial paralysis or recurrent paralysis, may occur in such cases.[11,12]

The integrity of facial nerve motor function in the setting of compression by adjacent eighth-nerve tumors is not easily explained. Jung et al[3] suggest that the nerve sheath provides a critical protective barrier. Their study of facial nerve tumors showed a correlation between tumor invasion through the nerve sheath and development of facial paralysis. In the absence of nerve sheath invasion, the facial nerve generally appears to tolerate gradual pressure stresses exceedingly well. Thus, it is doubtful that mass effect alone caused the original paralysis in our patient, since there were no other symptoms initially. Perhaps a local vascular compromise produced her facial paralysis. The finding of greatly diminished perineural vascularity in the region of the nerve compression, as was observed under the operating microscope, supports this view.

The finding of electrical excitability of the facial nerve after decompression at the time of surgery was unexpected. It again illustrates the resiliency of the nerve to local compression. Also, a limitation of electroneurogram testing is pointed out. A preoperative electroneurogram showing no response does not necessarily imply that the nerve is nonviable. Loss of the compound muscle action potential may be due to either actual neural degeneration or may reflect desynchrony within the facial nerve.[13,14] Desynchrony occurs during regeneration and may be present when the nerve is compressed or invaded by tumor. For this reason electroneurography is of prognostic value only during the acute phase of facial paralysis.[13]

A translabyrinthine approach was elected in anticipation of possible facial nerve grafting. This approach unexpectedly revealed schwannoma in the posterior aspect of the semicircular canal. Little attention has been given to distally situated schwannomas. Babin and Harker[15] described two cases of intralabyrinthine acoustic neuroma. They emphasized that an awareness of possible tumor in such usual sites is important in managing patients with retrocochlear lesions. Although the incidence of these intralabyrinthine tumors is unknown, long-term follow-up seems particularly warranted after hearing conservation procedures.

Magnetic resonance imaging is now the key imaging modality for evaluation of temporal bone soft-tissue masses.[16] The introduction of gadolinium diethylenetriamine pentaacetic acid, an intravenous paramagnetic contrast agent, has greatly improved the sensitivity of MRI in detecting small soft-tissue lesions of the internal auditory canal. While not specific for schwannoma, the gadolinium diethylenetriamine pentaacetic acid-enhanced MRI nevertheless provides a highly sensitive examination for masses of the cerebellopontine angle and internal auditory canal. We believe it has replaced air computed tomographic cisternography as the procedure of choice for suspected intracanalicular soft-tissue lesions.

In summary, vestibular schwannoma can present atypically with rapid-onset facial paralysis. Although this case is at the far end of the clinical spectrum for eighth-nerve schwannoma, it upholds Cawthorne's dictum regarding facial palsies. Any unexplained persistent facial paralysis should be evaluated by MRI with gadolinium contrast.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Four Years of Ophthalmology Training: Has Its Time Come?
John L. Keltner, MD (*Arch Ophthalmol.* 1990;108:35-36)

Should Postresidency Fellowships Be Mandatory?
David W. Parke II, MD (*Arch Ophthalmol.* 1990;108:37-39)

ROBERT E. FECHNER, MD, SECTION EDITOR

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PATHOLOGIC QUIZ CASE 1

LT Robert D. Wallace, MC, USNR; CDR Douglas M. Arendt, DC, USN; Richard T. Irene, MD, San Diego, Calif

A 39-year-old man presented with a 1-month history of progressive left nasal obstruction, epistaxis, and swelling of the lateral aspect of the nose and left cheek. He denied a history of tobacco or alcohol use and had no history of nasal surgery. A head and neck examination disclosed swelling over the left lateral nasal area and a left intranasal polypoid mass (Fig 1), but there was no evidence of bleeding or mucosal ulceration. The right nasal cavity and nasopharynx were clear. Sinus roentgenograms were normal. With the patient under local anesthesia, the polypoid mass, which was found to be arising from the nasal septum, was removed and was subsequently submitted for histologic examination (Figs 2 and 3).

What is your diagnosis?

PATHOLOGIC QUIZ CASE 2

CPT Richard F. Debo, MC, USA; CPT Martin Davidson, MC, USA; MAJ Carl A. Patow, MC, USA, Washington, DC

A 32-year-old black man presented with a 4-month history of a nontender right parotid gland swelling (Fig 1). An enzyme-linked immunosorbent antibody assay revealed antibodies to human immunodeficiency virus (HIV). The presence of HIV was confirmed by Western blot. The Walter Reed staging classification was WR3.[1] Physical examination revealed a 1-cm right postauricular lymph node and a 3 × 3-cm, cystic, right parotid mass. Serous fluid (10 mL) was obtained by needle aspiration, and cytologic evaluation revealed only occasional clusters of anaerobic epithelial cells and lymphocytes. Aerobic, anaerobic, mycobacterial, and fungal cultures were sterile. Two weeks after the initial aspiration, the fluid reaccumulated. A superficial parotidectomy was performed (Fig 2).

What is your diagnosis?

PATHOLOGIC QUIZ CASE 1

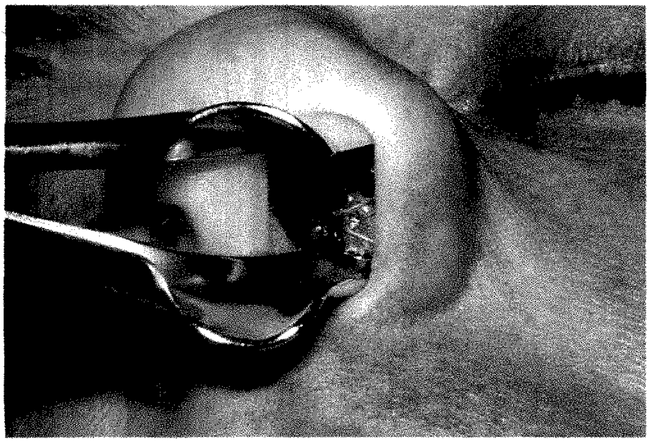


Figure 1.

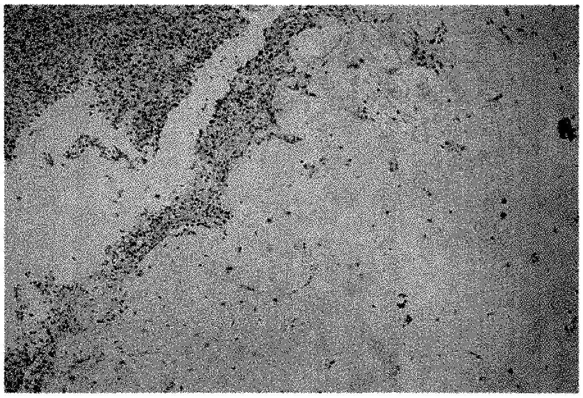


Figure 2.

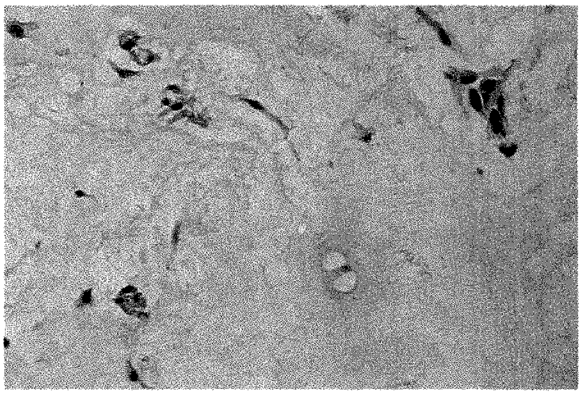


Figure 3.

PATHOLOGIC QUIZ CASE 2

Figure 1.

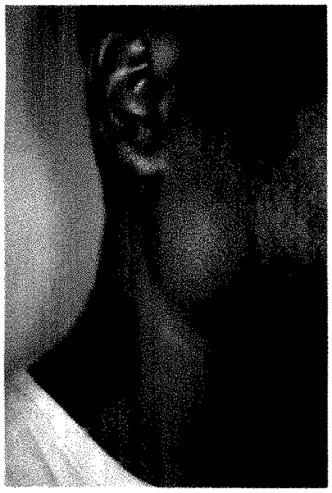


Figure 2.

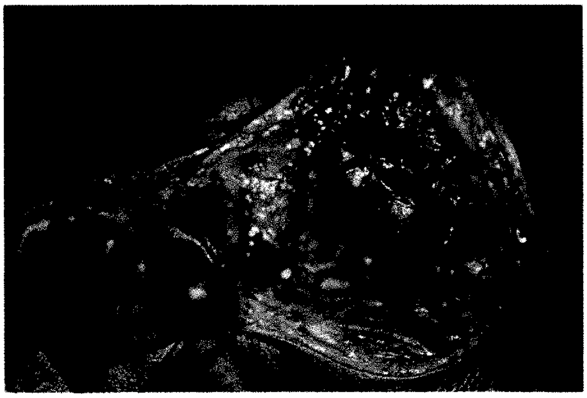


Figure 3.

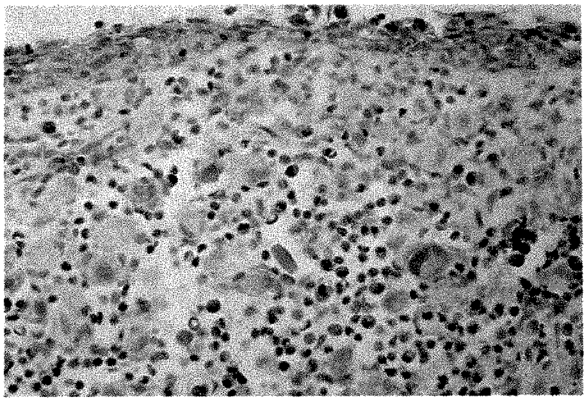
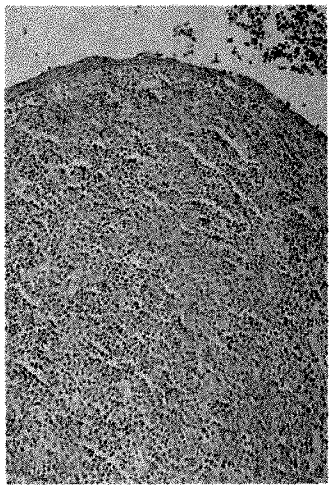


Figure 4.



Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 1

Pathologic Diagnosis: Pleomorphic adenoma.

Mixed tumor of the nasal septum was first reported by Denker and Kahler in 1929.[1] There have been approximately 20 cases reported in the literature since then. The largest series of intranasal mixed tumors was reported by Compagno and Wong[2] of the Armed Forces Institute of Pathology, Washington, DC.

Mixed salivary gland tumor, or pleomorphic adenoma, is usually a tumor of major salivary glands, yet it has been reported at various locations in the upper respiratory tract.[3] The occurrence varies, depending on the series and site. The rate of occurrence ranges from 6.5% to 20% in the upper respiratory tract. Batsakis[6] states that the most common site in the upper respiratory tract is the nasal cavity, followed by the maxillary sinus and the nasopharynx. The nasal septum is sparsely populated with salivary glands. The majority of intranasal mixed tumors arise from the septum, even though anatomically most of the minor salivary glands are located in the lateral nasal wall and turbinates.

There is no distinct age for presentation of this lesion, and it does not demonstrate the typical female predominance of mixed tumors in major salivary glands. The presenting complaints of the patient in this report were similar to those in prior reports.[7,8] In the majority of cases, unilateral nasal obstruction was the most common complaint.

The list of differential diagnoses for unilateral nasal polypoid masses is long. There have been numerous reports of benign and malignant tumors in this region. In this case, the smooth surface, lack of ulceration, and lack of bony destruction favored a benign neoplasm. Although pleomorphic adenomas are benign, their surgical treatment is complicated by a high recurrence rate if complete excision is not achieved. In the series reported by Compagno and Wong,[2] there was a 10% recurrence rate. This is relatively low compared with the rates reported for parotid and intraoral mixed tumors.[9] Thus, Compagno and Wong recommended conservative surgical therapy for pleomorphic adenomas, in contrast to previous authors who recommended a more radical surgical approach. In reviewing the histologic characteristics of recurrent mixed tumors, Compagno and Wong[2] found a high association with myxoid stroma, which can easily spill into the surgical field and thereby account for later recurrence. When they reviewed the intranasal lesions, a very cellular pattern was seen and myxoid stroma was uncommon.

Although pleomorphic adenoma of the nasal septum is an uncommon tumor, it is usually predictable, with a distinctive clinical presentation and course. Therefore, conservative management with lifelong follow-up is the treatment of choice, with radical surgical procedures reserved for locally aggressive or recurrent tumors.

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Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 2

Pathologic Diagnosis: Benign lymphoepithelial cyst of the parotid gland associated with HIV infection.

Benign lymphoepithelial cysts of the parotid gland were described prior to the acquired immunodeficiency syndrome (AIDS) epidemic,[2] particularly in association with Sjögren's syndrome. Two recent series have reported a total of 32 cases of cystic lesion of the parotid gland in patients with AIDS.[4,5] Shugar et al[4] have proposed that patients with these cysts and cervical adenopathy be considered to have AIDS until proved otherwise.

Patients with HIV infection and benign lymphoepithelial cysts present with asymptomatic unilateral or bilateral parotid gland enlargement. The cysts are most commonly found in the tail of the parotid gland. Computed tomographic scans with contrast injection typically demonstrate multiple cystic lesions with peripheral rim enhancement. The yellow serous fluid obtained on needle aspiration is microscopically consistent with a benign lymphoepithelial lesion.

On gross examination the lining of the cyst is shiny, with multiple smooth mucosal projections. The histopathologic appearance is that of a large epithelial-lined cyst surrounded by lymphoid tissue containing large germinal centers (Fig 3). The epithelial lining is usually cuboidal and occasionally squamous. A dense infiltrate of lymphoid cells is found in the mucosal lining (Fig 4). The germinal centers deep to the epithelium displace the epithelium into the lumen of the cyst, producing mucosal projections into the cyst.

Several theories on the etiology of these cysts have been proposed. The follicular hyperplasia of the lymphatic tissue within the cyst lining is histologically identical to the lymphoid hyperplasia seen in other sites in patients with AIDS.[7] Finfer et al[5] have proposed that the follicular hyperplasia produces salivary ductal obstruction. Shugar et al[4] have suggested that the unique embryologic development of the parotid gland and periparotid lymph nodes may be a contributing factor.

Both lymphoma[7] and Kaposi's sarcoma[5] have been found unexpectedly in resected parotid cysts. Because patients with AIDS have an increased incidence of malignancy, the currently suggested treatment of benign lymphoepithelial cysts in HIV-infected patients is surgical excision. This recommendation should be applied on an individual basis, as surgery for HIV-infected patients holds special risks for both patient and surgeon.

The statements contained herein are the opinions of the authors and are not to be construed as official policy of the US Army or the Department of Defense.

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Residents and fellows in otolaryngology are invited to submit quiz cases for this section and to write letters to the ARCHIVES *commenting on cases presented. Quiz cases should follow the patterns established and must be submitted in duplicate. Photomicrographs must be clear and can include an outline drawing with important structures labeled, especially in the case of histopathology of the ear. Illustrations must be submitted as positive color transparencies (35 mm preferred). Do not submit color prints unless accompanied by original transparencies. Transparencies should be carefully packaged in a separate container. Please do not submit glass-mounted transparencies or the actual glass histology slides. Material for the Resident's Page should be mailed to the Chief Editor.*

Reprints not available.

Letters to the Editor

On the Cause of Sinusitis in Patients With Cleft Palate

To the Editor.—In our practice there is indeed a high incidence of sinusitis in patients with cleft palate. Chronic sinusitis commonly does not present with fever or headache, and must be ruled out in every patient with middle ear disease,[1,2] or bronchial asthma.[3] In our palate clinic every patient is examined with the aim of excluding sinusitis, and, if found, it is actively treated. In recent years, endoscopy has completely changed the diagnostic approach to paranasal sinus disease and its treatment.[4-6] By the use of endoscopy intranasal structures such as the ethmoidal system, including the bulla ethmoidalis, infundibulum, frontal recess, and the maxillary ostium, can be observed. Specific pathologic conditions can be diagnosed and appropriate treatment may be given.[4-6]

Ishikawa et al,[7] in their article recently published in the ARCHIVES, have studied this subject. They found an impairment of mucociliary clearance in their patients with cleft palate. This finding could be implicated as a causative factor of sinusitis in these patients. This report, however, raises some questions regarding the basic study performance, and the conclusions derived therefrom.

1. The authors have performed nasendoscopic examination of the velopharyngeal valve of their patients with no regard to the intranasal structures. In turn, they have examined their patients by anterior rhinoscopy only. Nasendoscopy should be performed by advancing the endoscope into the nasal cavity, thus completing endonasal endoscopy.
2. The authors based the diagnosis of sinusitis on regular roentgenograms. As the sinus system and especially the ethmoidal cells are a tridimensional labyrinth, regular roentgenograms are of limited diagnostic value.[8-10] More accurate roentgenographic studies must include computed tomography.[8-10] The authors should also indicate what their criteria are for diagnosis of sinusitis—an air-fluid level only, or also thickening of the nasal mucosa? In our experience, purulent discharge from the sinus ostia can be seen on endoscopy, in the presence of normal roentgenograms, and the sinusitis is confirmed only by computed tomography.[11]
3. No details of the endoscopic examination of the velopharyngeal valve are reported. How do the authors define the grading of velopharyngeal competency? All 28 patients who underwent pharyngeal flap surgery are indicated in Fig 4: "with pharyngeal flap." This kind of surgery has a limited success.[12-14] Generally, there are flaps undergoing breakdown, and others become too narrow. In cases of a velopharyngeal valve with poor or no palate or lateral-wall mobility, a large flap with limited cross area of the velopharyngeal valve at rest is needed for competent speech.[13,14] Drainage of the postnasal drip and nasal respiration depend on the cross area of the velopharyngeal valve at rest, ie, in breathing.
4. The authors found impairment of nasal clearance function and impaired ciliary activity in their patients with cleft palate. How can they ascertain whether the impairment of the mucociliary clearance is the cause of sinusitis and not secondary to the rhinitis caused by chronic sinusitis?
5. The authors stated that they also did rhinomanometry (p 442), but they do not report results of this measurement.

In conclusion, the high prevalence of paranasal disease in patients with cleft palate is of great importance and interest. Although the article of Ishikawa et al[7] is of importance, the question about the cause of sinusitis still remains open and needs further study.

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In Reply.—The following comments are offered in response to Dr Finkelstein and coworkers' letter to the editor.

1. A flexible fiberscope (Olympus PNF-type 2), with a diameter of 3.4 mm, was used to examine velopharyngeal function. In our study, a large number of subjects were young and even in these subjects it was easy to examine the velopharynx. However, examination of intranasal structures such as the maxillary ostium and the ethmoidal system was difficult in younger subjects. Therefore, the diagnosis of sinusitis was based on the findings obtained by anterior rhinoscopy and roentgenography.
2. Computed tomography is commonly used for examination of paranasal sinus diseases in our institution. However, computed tomography is not recommended for all younger subjects because exposure to radioactive rays should be minimized at this age. Furthermore, plain roentgenograms are as useful as computed tomography in the diagnosis of nasal sinusitis.

In the present study, the criteria for diagnosis of sinusitis were thickening of the sinus mucosa, the air-fluid level, and opacification.

3. In the endoscopic examination, velopharyngeal function was graded as follows: (1) complete closure, in which the velopharynx was completely closed during phonation of Japanese vowels and consonant-vowel syllables; (2) slight incomplete closure, in which bubbling or a slight gap was noted; and (3) incomplete closure when there was a distinct gap.

The pharyngeal flap operation was useful for correction of velopharyngeal inadequacy. In our hospital, high attachment and folded pharyngeal flap operations were often performed. A folded pharyngeal flap without a raw surface permits minimal shrinkage and scar contracture of the flap, and effective velopharyngeal closure is usually achieved.[1-3]

4. A saccharin test was performed in 91 noses of patients with cleft palate (Fig 7). These patients were divided into those with and those without sinusitis. In the former group, 28 (75.7%) of 37 noses showed saccharin times over the normal upper limit or 11 minutes. In the latter group, 24 (44.4%) of 54 noses exceeded the upper limit. Thus both groups showed significantly longer saccharin times ($P < .01$). This indicates that impaired mucociliary function is the cause of sinusitis in patients with cleft palate.

Several investigators reported a relationship between nasal mucociliary clearance and nasal airway patency.[4-6] In patients with cleft palate who have an increased nasal airway resistance, as reported previously,[7-9] nasal obstruction may induce impaired mucociliary clearance.

5. Rhinomanometry was performed by the active-anterior method using a rhinoconductance meter (RION SR-10). Nasal resistance was calculated at a fixed pressure of 100 Pa during inspiration. The total nasal resistance in normal subjects was 0.402 ± 0.134 Pa/cm^3 per second in those 3 to 6 years of age, 0.298 ± 0.099 Pa/cm^3 per second in those 7 to 15 years, and 0.268 ± 0.118 Pa/cm^3 per second in those 16 to 40 years. In contrast, the respective values in patients with cleft palate were 0.621 ± 0.299 Pa/cm^3 per second, 0.588 ± 0.390 Pa/cm^3 per second, and 0.405 ± 0.278 Pa/cm^3 per second. Nasal airway resistance was significantly higher ($P < .01$) in patients with cleft palate than in normal subjects.

It was speculated that intranasal deformities such as deviation of the nasal septum and hypertrophy of the inferior turbinate increase nasal resistance in patients with cleft palate.

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News and Comments

Request for Proposals From the American Laryngological Association.—The American Laryngological Association has established a grant for research on laryngology, rhinology, and related subjects. The maximum grant for 1 year is $15 000. Deadline for submission is June 1, 1990. For the specifics of eligibility and application materials, contact H. Bryan Neel III, MD, Secretary, American Laryngological Association, 200 First St SW, Rochester, MN 55905.

International Conference on Immunobiology.—The Third International Academic Conference Immunobiology in Otology, Rhinology, and Laryngology will be held in Coronado, Calif, from November 8 through 10, 1990. A limited number of free papers will be accepted by the program committee. During the 3-day conference, a permanent poster session will be organized in the hall of the conference site. For further information, contact Jan E. Veldman, MD, PhD, Secretary General, c/o Kugler & Ghedini Congresses, PO Box 516, NL-1180 AM, Amstelveen, the Netherlands; (+31.20) 278-070; fax (+31.20) 380-524; or Kugler & Ghedini Congresses, PO Box 5794, Berkeley, CA 94705-5794; fax (818) 363-7210.

Academy Announces Its Course Schedule.—The American Academy of Facial Plastic and Reconstructive Surgery announces its course schedule for the third and fourth quarters of 1990. The course schedule is as follows: June 1 and 2, "Soft-Tissue Workshop," in Santa Barbara, Calif; June 4 through 8, "Microvascular Workshop for Otolaryngologists," in Ann Arbor, Mich; June 17 through 21, "Rhinoplasty and Otoplasty," in New York, NY; June 22 and 23, "Cosmetic Surgery of the Aging Eye," in New York; June 25 and 26, "Facelift Surgery," in New York; July 30 and 31, "Basic Rhinoplasty," in Portland, Ore; August 1 through 5, "Advanced Rhinoplasty," in Portland, Ore; October 12 through 14, "Craniofacial," in Santa Rosa, Calif; and October 18 through 21, "Facial Skin Malignancies," in Seattle, Wash.

F. T. Hill Seminar in Otolaryngology.—This year's F. T. Hill Seminar includes discussions of nasal surgery, management of the difficult nose, skull base surgery, cochlear implants, the patient with dizziness, video stroboscopy, surgery for vocal rehabilitation, laryngeal framework surgery, and other topics of current interest. The director of the seminar is Loring W. Pratt, MD. There will be 18 hours of Category 1 credit available. Families are welcome, and meals and lodging are available. For further information, contact R. H. Kany, Director of Special Programs, Colby College, Waterville, ME 04901; (207) 872-3386.

Instructions for Authors

NOTE: ***Please read these instructions carefully—technical deficiencies must be corrected before manuscripts can be reviewed.***

Send manuscripts by first-class mail to Byron J. Bailey, MD, Chief Editor, *Archives of Otolaryngology—Head & Neck Surgery,* Substation 1, PO Box 103, Galveston, TX 77550. Phone: (409) 765-9040. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of the ARCHIVES and may not be published elsewhere without permission from the publisher (AMA).

Any manuscript, Letter to the Editor, or other material sent for publication must be accompanied by a letter containing the following language: "In consideration of the American Medical Association's taking action in reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the AMA in the event that such work is published by the AMA." We regret that transmittal letters not containing the foregoing language *signed by all authors* of the submission will necessitate delay in the review of the manuscript.

In case the work was done by a federal employee, each author must include a signed statement that the work reported was done while he or she was employed by the federal government.

Author Responsibility.—All accepted manuscripts are subject to copy editing. The author will receive an edited typescript and layout rather than galley or page proofs for approval. The author is responsible for all statements in his work, including changes made by the copy editor.

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Abstract (Second Page).—Provide a double-spaced abstract (135-word maximum) of the article. Abstract should include statements of problem, method of study, results, and conclusions. Do not include a "summary" section in the main manuscript.

Manuscript Preparation.—Submit the original typed manuscript **plus** two high-quality copies of the entire manuscript. *The entire manuscript,* including abstract, references, legends, and tables, *must be typewritten, double-spaced,* on 21.6 × 27.9-cm (8½ × 11-in) heavy-duty white bond paper. Ample margins of at least 2.5 cm (1 in) should be provided. Do not justify the right margin if a word processor is used.

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Consent Forms.—Manuscripts reporting the results of experimental investigations of human subjects must include a statement to the effect that informed consent was obtained after the nature of the procedure(s) had been fully explained.

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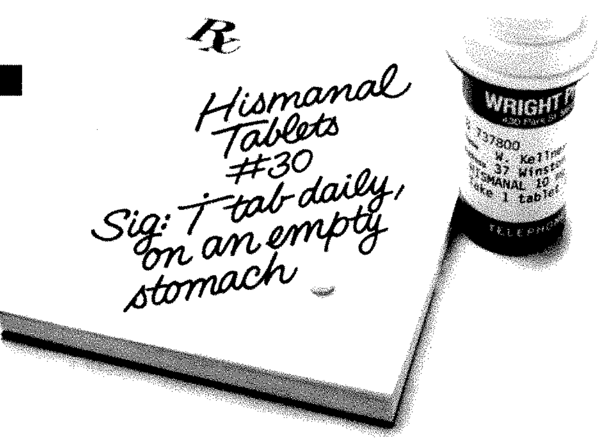

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DESCRIPTION

HISMANAL® (astemizole) is a histamine H_1-receptor antagonist available in scored white tablets for oral use.

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General: Caution should be given to potential anticholinergic (drying) effects in patients with lower airway diseases, including asthma.

Caution should be used in patients with cirrhosis or other liver diseases (See Clinical Pharmacology section).

HISMANAL does not appear to be dialyzable.

Caution should also be used when treating patients with renal impairment.

Information for Patients: Patients taking HISMANAL should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting HISMANAL therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby (see Pregnancy subsection). Patients should be instructed 1) to take HISMANAL only as needed, 2) not to exceed the prescribed dose, and 3) to take HISMANAL on an empty stomach, e.g., at least 2 hours after a meal. No additional food should be taken for at least 1 hour post-dosing. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic potential has not been revealed in rats given 260x the recommended human dose of astemizole for 24 months, or in mice given 400x the recommended human dose for 18 months. Micronucleus, dominant lethal, sister chromatid exchange and Ames tests of astemizole have not revealed mutagenic activity.

Impairment of fertility was not observed in male or female rats given 200x the recommended human dose.

Pregnancy: Pregnancy Category C: Teratogenic effects were not observed in rats administered 200x the recommended human dose or in rabbits given 200x the recommended human dose. Maternal toxicity was seen in rabbits administered 200x the recommended human dose. Embryocidal effects accompanied by maternal toxicity were observed at 100x the recommended human dose in rats. Embryotoxicity or maternal toxicity was not observed in rats or rabbits administered 50x the recommended human dose. There are no adequate and well controlled studies in pregnant women. HISMANAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Metabolites may remain in the body for as long as 4 months after the end of dosing, calculated on the basis of 6 times the terminal half-life (See Clinical Pharmacology section).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because certain drugs are known to be excreted in human milk, caution should be exercised when HISMANAL is administered to a nursing woman. HISMANAL is excreted in the milk of dogs.

Pediatric Use: Safety and efficacy in children under 12 years of age has not been demonstrated.

ADVERSE REACTIONS

The reported incidences of adverse reactions listed in the following table are derived from controlled clinical studies in adults. In these studies the usual maintenance dose of HISMANAL® (astemizole) was 10 mg once daily.

	Percent of Patients Reporting		
	Controlled Studies*		
ADVERSE EVENT	Hismanal (N = 1630) %	Placebo (N = 1109) %	Classical** (N = 304) %
Central Nervous System			
Drowsiness	7.1	6.4	22.0
Headache	6.7	9.2	3.3
Fatigue	4.2	1.6	11.8
Appetite increase	3.9	1.4	0.0
Weight increase	3.6	0.7	1.0
Nervousness	2.1	1.2	0.3
Dizzy	2.0	1.8	1.0
Gastrointestinal System			
Nausea	2.5	2.9	1.3
Diarrhea	1.8	2.0	0.7
Abdominal pain	1.4	1.2	0.7
Eye, Ear, Nose, and Throat			
Mouth dry	5.2	3.8	7.9
Pharyngitis	1.7	2.3	0.3
Conjunctivitis	1.2	1.2	0.7
Other			
Arthralgia	1.2	1.6	0.0

*Duration of treatment in Controlled Studies ranged from 7 to 182 Days

**Classical Drugs: Clemastine (N = 137); Chlorpheniramine (N = 100); Pheniramine Maleate (N = 47); d-Chlorpheniramine (N = 20)

Adverse reaction information has been obtained from more than 7500 patients in all clinical trials. Weight gain has been reported in 3.6% of astemizole treated patients involved in controlled studies, with an average treatment duration of 53 days. In 46 of the 59 patients for whom actual weight gain data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported in clinical trials or spontaneously from marketing experience with HISMANAL include: angioedema, bronchospasm, depression, edema, epistaxis, myalgia, palpitation, photosensitivity, pruritus, and rash.

Marketing experiences include isolated cases of convulsions. A causal relationship with HISMANAL has not been established.

OVERDOSAGE

In the event of overdosage, supportive measures including gastric lavage and emesis should be employed. Cases of overdose have been reported from foreign marketing experience. Although overdoses of up to 500 mg have been reported with no ill effects, cases of serious ventricular arrhythmias, including Torsades de pointes, following overdoses of greater than 200 mg have been reported. Patients should be carefully observed and ECG monitoring is recommended in cases of suspected overdose. An appropriate antiarrhythmic treatment may be needed. HISMANAL does not appear to be dialyzable.

Care should be taken not to exceed dosing recommended in the DOSAGE AND ADMINISTRATION section.

Oral LD_{50} values for HISMANAL were 2052 mg/kg in mice and 3154 mg/kg in rats. In neonatal rats, the oral LD_{50} was 905 mg/kg in males and 1235 mg/kg in females.

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U.S. Patent 4,219,559 December 1988
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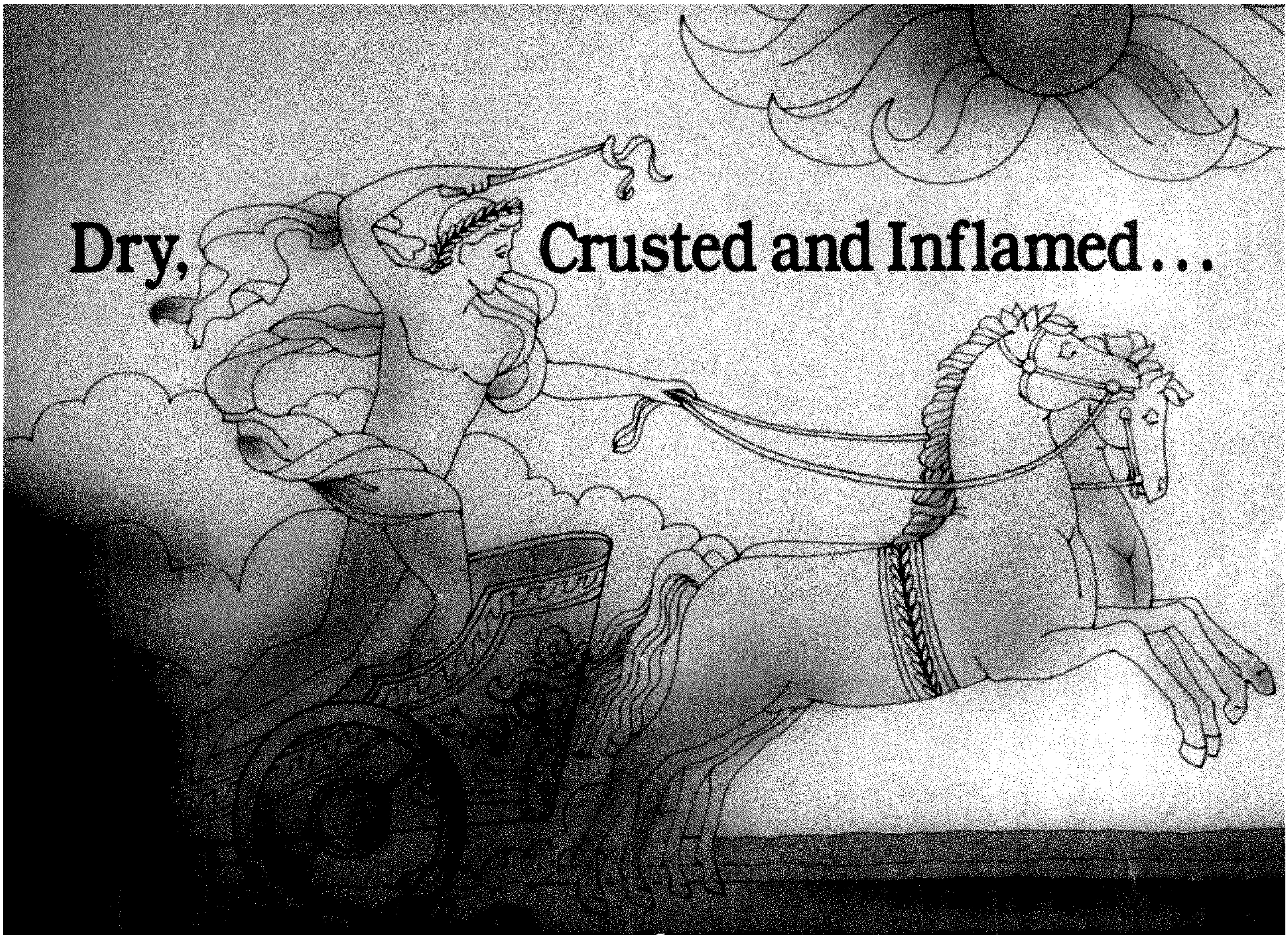

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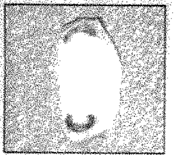

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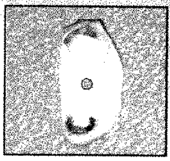

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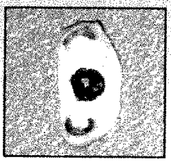

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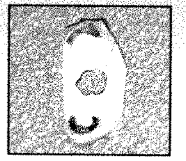

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Inquiries about "BOX NUMBER" advertisements: All replies must be in writing and must cite the box number in the ad. Example: Box _____, c/o AOTO, P.O. Box 1510, Clearwater, Florida 34617. We are not permitted to divulge the identity of advertisers who wish their mail sent in care of Archives of Otolaryngology.

CLASSIFIED INFORMATION

Regular Classified	1 Time	3 Times or more*
Cost per word	$1.50	$1.35
Minimum 20 words.		per issue

**In order to earn the three-time rate, your ad must be placed and prepaid at the same time for three or more issues.*

Counting Words: Two initials are considered one word, each abbreviation is considered one word, and figures consisting of a dollar sign and five numerals or less are considered one word. Cities and states consisting of two words or more are counted as one word: i.e., "New York" and "Salt Lake City." Zip code is considered one word and must appear in all ads. Telephone number with area code is considered one word. When box numbers are used for replies, the words "Box _____, c/o AOTO" are to be counted as three words.

Classified Display	1 Time	3 Times
Full page	$555	$511
Two-thirds page	475	437
One-half page	419	386
One-third page	333	306
One-sixth page	222	204
Column inch	50	45

Minimum display ad: one column inch
12-time rate available on request.

Closing Date

The 25th of the second month prior to issue date. Example: The November issue closes September 25th. No ads can be cancelled after the closing date.

Send all copy, correspondence, production materials and payments to:

archives of
Otolaryngology–
Head & Neck Surgery
Classified Department
P.O. Box 1510, Clearwater, Florida 34617

For assistance with your ad schedule call toll free:
National 800-237-9851
Florida 800-553-8288 □ Local 813-443-7666

Professional Opportunities

OTOLARYNGOLOGIST — Virginia. Modern 153-bed acute care hospital has an excellent opportunity for a board-certified/-eligible otolaryngologist. Medical service area population of 55,000. New office building available. Very competitive financial package and relocation. Beautiful mountainous plateau area 50 miles from Roanoke, with exceptional cultural, educational and recreational opportunities. Contact: Assistant Administrator, P.O. Box 759, Pulaski, VA 24301. (703) 980-6822.

Professional Opportunities

OTOLARYNGOLOGIST — BC/BE to join main branch of thirty-five physician, multi-specialty group. Excellent clinic and hospital facilities. Very competitive salary and benefit package. Excellent opportunity. Good hunting, fishing. Good schools, a beautiful place to raise a family. Call Executive Administrator collect, (701) 857-0236. Or write: Medical Arts Clinic, P.C., P.O. Box 1489, Minot, ND 58702-1489.

OTOLARYNGOLOGIST
Board-certified or Board-eligible

Otolaryngologist to join a busy, young, established solo practitioner in a growing community with excellent schools, housing and all recreational activities. Modern, well-equipped office located 60 miles southeast of Chicago.

Competitive salary and benefits.
Please send curriculum vitae to:

Mohammad K. Arab, MD, F.A.C.S.
1300 State Street, Suite 2C
LaPorte, IN 46350

NORTHEASTERN Pennsylvania/Poconos — 66 physician, multi-specialty group seeks second BE/BC otolaryngologist. Salary with incentive, excellent benefit package. CV to: Richard Somma, MD, Geisinger Medical Group, 1010 East Mountain Drive, Wilkes-Barre, PA 18702.

OTOLARYNGOLOGIST
Durham, North Carolina

Private Eye, Ear, Nose and Throat Hospital and Clinic in Piedmont, North Carolina looking for fourth otolaryngologist in busy private practice with academic affiliation. Prefer otology background. Please send curriculum vitae or call: Charles H. Mann, MD, Department of Otolaryngology, McPherson Hospital, 1110 West Main Street, Durham, NC 27701. (919) 682-9341.

77 PHYSICIAN MULTI-SPECIALTY group seeks BC/BE ENT physician. Excellent fringe benefits. Full association possible within three years. This group is located in the far western suburbs of Chicago in an area offering excellent schools, housing and recreational facilities. Send CV to: Box #403, c/o AOTO.

OTOLARYNGOLOGIST

Board-certified/board-eligible otolaryngologist needed for busy four-person practice in Milwaukee. Outstanding opportunity in well known group practicing all aspects of our specialty. Send CV to:

RUSSELL S. YALE, MD
10520 North Port Washington Road
Milwaukee, WI 53092. (414) 241-8000

WALNUT CREEK, CALIFORNIA — We are seeking a BC/BE general otolaryngologist to join three-person department. High-growth, white collar suburban Bay area. Fully referred, broad spectrum practice. Experienced or 1990 graduate considered. For more information, please send CV to: Glenn Schneider, MD, The Permanente Medical Group, Inc., 1425 South Main Street, Walnut Creek, CA 94596. EOE.

PLEASE NOTE—Address replies to box number ads as follows: Box number, _____, c/o AOTO, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

OTOLARYNGOLOGY Consultants of Memphis — Expanding three-doctor group seeks pediatric, fellowship-trained associate to join a diverse, quality oriented and busy practice. Four fully staffed offices. Associated with the areas major medical centers. Competitive salary and comprehensive benefits. Opportunities leading to partnership after two years. Please direct inquiries and CV to: Thomas E. Long, MD; Rande H. Lazar, MD, 848 Adams, Suite 401, Memphis, TN 38103.

MAINE COAST Otolaryngologist — Private practice for well-qualified, motivated ENT physician. Guaranteed cross coverage. Campus office space with new equipment. Affiliate with 106-bed, medical referral center. Live and work in beautiful and desirable coastal community. Send CV to: New England Health Search, 63 Forest Avenue, Orono, ME 04473. Or call: (207) 866-5680 or (207) 866-5685.

CALIFORNIA — Santa Barbara

72-physician, multi-specialty group seeks BC/BE ENT physician to join busy practice. Excellent compensation and benefits package including malpractice insurance, CME and educational allowance.

Send CV to: Barbara Volk
Santa Barbara Medical Foundation Clinic
P.O. Box 1200, Santa Barbara, CA 93102.

OTOLARYNGOLOGIST — Head and Neck Surgery. The Department of Surgery of the Kern Medical Center is seeking a second full-time staff otolaryngologist. Kern Medical Center is a 185-bed community hospital with a residency training program in surgery, medicine, OB/GYN, and emergency medicine. The Department of Surgery is affiliated with the University of California at San Diego. The position involves all aspects of otolaryngology, head and neck surgery and includes participation in residency training as well as private practice. Send inquiries with your curriculum vitae to: Richard F. Busch, DDS, MD, Division of Otolaryngology, Department of Surgery, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. (805) 326-2274.

ATTENTION PHYSICIAN RECRUITERS. The "Classified Advertising" sections now in all nine AMA Specialty Journals target the physician you want. These highly visible sections put your message in the hands of every specialist that qualifies for your professional opportunity, every month. To place the ad of your choice, any size, call toll free: (800) 237-9851; or in Florida (800) 553-8288.

OTOLARYNGOLOGY Consultants of Memphis - Expanding three doctor group seeks facial plastic, fellowship-trained associate to join a diverse, quality oriented and busy practice. Four fully staffed offices. Associated with the areas major medical centers. Competitive salary and comprehensive benefits. Opportunities leading to partnership after two years. Please direct inquiries and CV to: Thomas E. Long, MD; Rande H. Lazar, MD, 848 Adams, Suite 401, Memphis, TN 38103.

Faculty Positions

CHAIRMAN, Department of Otolaryngology — Jefferson Medical College seeks a chairman of otolaryngology. Successful candidate will be an outstanding teacher, researcher and clinician. Minorities and women are encouraged to apply; equal opportunity employer, affirmative action. Send curriculum vitae and three references to: Joseph L. Seltzer, MD, Professor and Chairman of Anesthesiology, Jefferson Medical College, 111 South 11th Street, Philadelphia, PA 19107.

Faculty Positions

OTOLARYNGOLOGIST (head and neck oncologic and reconstructive surgery). Unlimited practice and research opportunities in active, high volume, multidisciplinary head and neck cancer program in university-based hospitals. Exceptional life style and investment opportunities in sun belt community at assistant, associate or professor level; salary commensurate with appointment. Applicants should have major interests in reconstruction and exenteration in patients with head andneck cancer, as well as interest in general otolaryngology. Send CV to: J. Gail Neely, MD, Chairman, Department of Otorhinolaryngology, University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, OK 73190. Telephone: (405) 271-5504. Equal opportunity employer.

PEDIATRIC OTOLARYNGOLOGIST — Unlimited practice and research opportunities as chief of pediatric otolaryngology in large, free-standing, university-based pediatric hospital. Exceptional life style and investment opportunities in sun belt community. Assistant, associate or professor level; salary commensurate with appointment. Send CV to: J. Gail Neely, MD, Chairman, Department of Otorhinolaryngology, University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, OK 73190. Telephone: (405) 271-5504. Equal opportunity employer.

PEDIATRIC OTOLARYNGOLOGIST — A faculty position is available in otolaryngology at the Nemours Children's Clinic. We are seeking an individual who is board-certified and fellowship trained in pediatric otolaryngology and has a strong research and academic background. In addition to direct patient care responsibility, the position offers academic rank (assistant professor/associate professor) at a university affiliate setting of subspecialty clinical practice. Guaranteed salary and benefits will be commensurate to applicant's experience. Please send CV to: Bruce R. Maddern, MD, Nemours Children's Clinic, P.O. Box 5720, Jacksonville, FL 32247. Academic status is offered by the University of Florida, an equal opportunity/affirmative action employer with whom Nemours is affiliated.

OTORHINOLARYNGOLOGY/Head and Neck Surgery — Academic position. The Temple University School of Medicine of Philadelphia, Pennsylvania is seeking a board-certified/board-eligible otolaryngologist to join a rapidly expanding department of otolaryngology. A strong interest in resident and medical student teaching is desirable. Opportunities are available to participate in both clinical and basic research. Salary and academic appointment will be commensurate with experience and training. Benefits are excellent. An equal opportunity employer. Applicants should send their curriculum vitae to: Max L. Ronis, MD, Department of Otolaryngology, Temple University School of Medicine, 3400 North Broad Street, Philadelphia, PA 19140.

Practices Available

CENTRAL CONNECTICUT — Excellent opportunity to purchase well established general otolaryngology practice. Fully equipped and staffed office associated with a major area hospital. Current will assure a smooth transition. Principles only. Box #404, c/o AOTO.

Medical Equipment/Supplies

EQUIPMENT FOR SALE

Maico MA22 advanced diagnostic audiometer $300; Tracor Rudmose ARJ4c6 automatic recording audiometer $500; SMR mobile suction/pressure cabinet $500; Lempert-Storz headlight $150. Reliance Exam chair, electric, dark green $500. All items guaranteed. 1/2 million dollars in used medical equipment in stock. Write for complete list:

Dick Rice, Plaza Medical, Inc.
9780 East Girard, Denver, CO 80231. (303) 695-4441

Marketing

FREE PRACTICE-BUILDING fact sheet — "How to Build Your Practice Without Advertising". (800) 347-8172 (physicians only).

OTOLARYNGOLOGIST

Busy clinical and surgical practice seeks BC/BE otolaryngologist as second member of department.

Located in the northwestern suburbs of Minneapolis, offering suburban living with easy access to an unlimited array of family, cultural, educational and recreational opportunities.

Members of our multi-specialty group earn a highly competitive salary and excellent benefits including paid vacation and CME; pension and profit sharing plans; paid malpractice; health, life and disability benefits.

For further information contact:

W. EDWIN GOULD, MD
13986 Maple Knoll Way
Maple Grove, MN 55369
(612) 420-5700

OTOLARYNGOLOGIST

We are seeking a fourth well-qualified Otolaryngologist to join our expanding department. Our service now has two Attending Physicians as well as two Physician Assistants and Resident coverage. The department follows a multi-disciplinary approach, working closely with oncologists, radiotherapists, neurosurgeons, general surgeons, and speech pathologists and audiologists. Annual volume averages 6,000 outpatient visits, 275 admissions and 300 surgical procedures. The Mary Imogene Bassett Hospital is a regional referral and teaching center affiliated with Columbia University. Cooperstown enjoys recreational facilities, excellent schools, and a wide range of cultural and artistic activities. The village, one of the most visited in the U.S., is known for its museums, its air of history, pastoral beauty and its resort features. We provide a competitive salary, incentives and free benefits including malpractice, paid relocation, generous free time, conference leave and annuity participation paid at 15% of salary.

Please send CV and correspondence to:

Robert Dewell, M.D.
Chief, Otolaryngology
The Mary Imogene Bassett Hospital
One Atwell Road, Cooperstown, NY 13326
(607) 547-3261

THE MARY IMOGENE
BASSETT HOSPITAL

Otolaryngologist

Board-certified/-eligible otolaryngologist needed as associate to join an active four-physician section of otolaryngology, practicing all aspects of modern otolaryngology.

This 200-physician, multi-specialty clinic serves as a referral center for surrounding areas of northeastern Pennsylvania and the Southern Tier of New York State. Affiliated with progressive 366-bed hospital. State-of-the-art diagnostic and operative equipment available. Medical school teaching affiliation provides a stimulating environment.

Area provides attractive living conditions with ample seasonal recreation opportunities. Easy access to major metropolitan areas. Excellent salary and fringe benefits.

Respond with curriculum vitae to:

GUTHRIE CLINIC

Sayre, PA 18840 • (717) 888-5858

ATTENTION:
G.V. Ippolito, Vice President

THE PERMANENTE MEDICAL GROUP
NORTHERN CALIFORNIA

QUALITY
STABILITY
LEADERSHIP
GROWTH
SUPPORT
REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region for additional BC/BE Otolaryngologists.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. Please call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. AENT-7302, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800)777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

PARTNERS PRACTICING GOOD MEDICINE.

The Southern California Permanente Medical Group offers you the freedom to concentrate on patient care.

We are a well-established, prepaid health care program. Our multispecialty group practice is a successful partnership composed of and managed by SCPMG physicians.

Due to our recent growth, we are currently accepting applications from board eligible/certified **ENT/Head & Neck Surgeons** for clinical positions at Kaiser Permanente Medical Centers throughout Southern California.

Our compensation is competitive and benefits are outstanding. They include: professional liability, medical and dental coverage, vacation and sick leave, continuing education, life insurance and retirement plans. **After two years full-time employment, physicians are eligible to be considered for partnership.**

For a physician application, please call (800) 328-5278. If calling from outside of California, please call (800) 541-7946 or send your curriculum vitae to: Irwin P. Goldstein, M.D., Associate Medical Director, SCPMG, Dept. 016, Walnut Center, Pasadena, CA 91188-8013.

Equal Opportunity Employer M/F/H

KAISER PERMANENTE
Good People. Good Medicine.

Southwestern Michigan
Otorhinolaryngologist

Immediate opening for a board certified or board eligible Otorhinolaryngologist to join a very busy Otorhinolaryngology practice in Michigan. Please forward your curriculum vitae in confidence to: **Confidential Reply Service, Dept. O-SS, Thompson Recruitment Advertising, 3000 Town Center, Suite 1600, Southfield, MI 48075.** All replies will be forwarded to our client unopened. No phone calls please. Our client is an equal opportunity employer.

Pediatric Otolaryngology Fellowship

Available July 1991: One year of training. Extensive experience in all aspects of pediatric otolaryngology. This will include all phases of otology, laryngeal problems, laser surgery, maxillofacial surgery, facial plastic and reconstructive surgery, and endonasal surgery.

Opportunities for basic and/or clinical research are available and encouraged. Over 2,000 surgical procedures performed per year. A stipend, living allowance and insurance package is available.

Applications may be obtained by contacting:

Rande H. Lazar, MD
Director of Fellowship Training

Otolaryngology Consultants of Memphis
Department of Otolaryngology
Le Bonheur Children's Medical Center
Memphis, TN 38103

ACADEMIC POSITION IN OTOLARYNGOLOGY

Full-time, Assistant Professor, Department of Otolaryngology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo.

Teaching of medical students, residents and fellows, coverage of clinic at Veterans Administration Medical Center, director of departmental research and development, and Cell Culture Laboratory at Sisters of Charity Hospital, director of microsurgery and skull base laboratories as well as small animal laboratory. Active research program resulting in funding and publications. There must be a strong commitment to basic and clinical research and education.

Qualification: MD degree, board-certified/-qualified in otolaryngology, general surgery or plastic and reconstructive surgery and have completed a two-year fellowship in advanced head and neck oncologic surgery as approved by the Society of Head and Neck Surgeons and the American Society for Head and Neck Surgery. Must be licensed to practice in the state of New York. Preferred to have previous experience as attending in an academic environment. Contact:

John M. Lore, Jr., MD
Professor and Chairman
Department of Otolaryngology
2121 Main Street, Suite 205
Buffalo, NY 14214 • (716) 862-2783

SUNYAB is an equal opportunity/affirmative action employer and encourages the candidacies of women and minorities.

Otolaryngologist

BC/BE — Associate with well-established 31-MD multi-specialty group, located 45 miles from San Francisco and 20 minutes from Napa Valley in growing community serving 140,000. Patients include both fee-for-service and prepaid health plan.

Attractive compensation and benefits. Malpractice provided.

Send CV to:

Dominic Scolaro
Caller Box 4020
Fairfield, CA
94533-0410
(707) 426-3911

Academic Position in Otolaryngology

Full-time, Assistant Professor, Department of Otolaryngology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo.

Supervision of residents, performing otologic surgery, exposure of faculty and residents to neurotologic techniques and didactic instruction to members of the Department of Otolaryngology, and a specific and cooperative relationship and collaboration with the Department of Communicative Disorders and Science. There would be a further charge of developing cochlear implants and development and implementation of implantable hearing aids protocol; diagnosis and treatment of vestibular disorders.

Qualifications: Candidate must be board-certified in otolaryngology, have successfully completed a fellowship in neurotology and have at least one year experience in attending status in an academic environment. Must be licensed to practice in the state of New York. Contact:

John M. Loré, Jr., MD
Professor and Chairman
Department of Otolaryngology

2121 Main Street, Suite 205
Buffalo, NY 14214
(716) 862-2783

SUNYAB is an equal opportunity/affirmative action employer and encourages the candidacies of women and minorities.

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento, and the Central Valley.

OTOLARYNGOLOGIST

A position is currently available for a full time staff otolaryngologist in our South San Francisco facility. Includes office and operating room responsibilities.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including mortgage assistance, scheduled time off, malpractice insurance, and medical, dental and life insurance, and a substantial retirement program.

To inquire about this and other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. AO-SSF, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, California 94612. (415) 987-4949. We are an equal opportunity employer.

KAISER PERMANENTE
Good People. Good Medicine.

We Target The Physician You Want!

The Archives of Otolaryngology's classified recruitment advertising section is seen precisely by the physician you need – all otolaryngologists and head and neck surgeons. A total targeted physician audience of over 12,000.

Find the physician you need now. Send us your advertising order today. Just complete the coupon below and attach your typewritten copy. The next available issue is June which closes Wednesday, April 25th.

For complete advertising rate information, please see the first page of this section.

Insert my ad ______________ times, beginning

with the ______________________________ issue.

Place my ad under the heading

____

Enclosed is my check for $ ______________
to cover full payment of my advertising schedule.

Institution ______________________________

Contact Person ___________________________

Address ________________________________

City ___________________________________

State __________ Zip ____________________

Telephone Number _________________________

Authorized Signature _______________________

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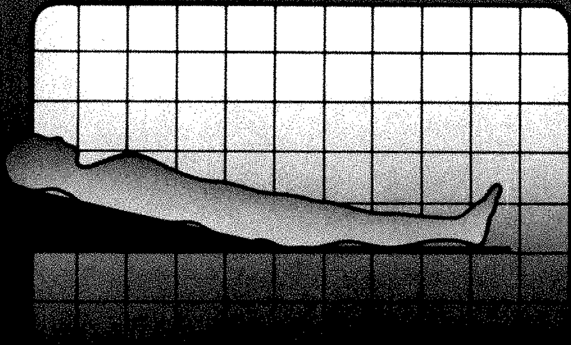
INTRODUCING



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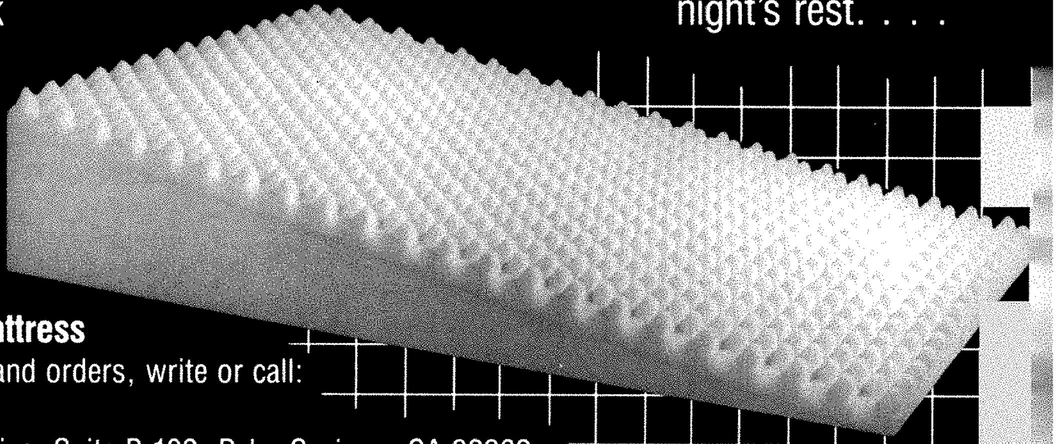
IN UNEXPLAINED COUGH, GLOBUS SENSATION
PERSISTANT THROAT CLEARING, OBSCURE PHARYNGITIS
NOCTURNAL COUGH AND WHEEZE...

...THINK OF GASTROESOPHAGEAL REFLUX!

When infection and neoplasm are excluded, where allergy is unlikely, and symptoms persist despite time and therapeutic trials, think of reflux.

When laryngoscopy shows typical findings of post- and interarytenoid inflammation, pachydermia and contact granuloma, think of reflux.

And when you think of acid reflux, think of BEDGE. The treatment of gastroesophageal reflux disease begins with postural, anti-gravity positioning to prevent acid regurgitation into the esophagus and pharynx. The Bedge provides ideal positioning. It's long enough to affect the critical EG junction area, wide firm and comfortable for a good night's rest. . . .



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The Anti-Reflux Mattress

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For the most illuminating material available on the care of the voice . . .

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PUBLICATIONS

SYMPOSIUM TRANSCRIPTS

Symposium proceedings are published in the official journal publication of The Voice Foundation, ***Journal of Voice,*** *available from Raven Press, 1185 Avenue of the Americas, New York, NY 10036. Published quarterly. Subscription price:*
Individuals — $75.00 (U.S.) $89.00 (Non-U.S.)
Institutions — $89.00 (U.S.) $103.00 (Non-U.S.)
Single copy — $26.00

From the proceedings prior to the 1985 14th Symposium, transcripts of each symposium are published in two volumes: one volume contains the scientific papers presented at the symposium, the second volume contains the pedagogic and medical material. Available in sets or individually.

OTHER PUBLICATIONS

Spastic Dysphonia: State of the Art 1984
Edited by George A. Gates, M.D.

Transcripts of Panel Discussion, International Symposium on the Larynx, University of California, School of Medicine, San Francisco, California. 42pp. Softbound $15.00 U.S.

AUDIO VISUAL CASSETTES
— NEW! —

Diversity of the Normal Larynx
by Janina Casper, Ph.D., Raymond H. Colton, Ph.D. and David W. Brewer, M.D.

20 minutes, color and sound, $65.00 (U.S.) (NTSC only)

Dynamics of the Singing Voice
by Dr. Rafael Garcia-Tapia

20 minutes, color and sound, $65.00 U.S. (NTSC) $125.00 U.S. (PAL-SECAM)

Laryngostroboscopy and Phonosurgery
by Guy Cornut, M.D., Marc Bouchayer, M.D. and Hans Hartmann

24 minutes, color and sound, $65.00 U.S. (NTSC)

Phonosurgery on Singers
by Guy Cornut, M.D. and Marc Bouchayer, M.D.

25 minutes, color and sound, $65.00 U.S. (NTSC)

Also available is a library of 26 audio visual cassettes that covers a variety of voice related topics. Available in 3 sizes: ¾ " U-Matic, ½ " VHS and ½ " Beta. All sizes in NTSC and PAL-SECAM formats.

For more detailed information on publications and audio visual cassettes, please write:

The Voice Foundation
40 West 57th Street, Room 300
New York, New York 10019

RYNATAN® B.I.D.
TITRATABLE TABLETS

Each capsule-shaped tablet contains: phenylephrine tannate, 25 mg; chlorpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

RYNATAN®-S* B.I.D.
PEDIATRIC SUSPENSION

Each teaspoonful (5 mL) contains: phenylephrine tannate, 5 mg; chlorpheniramine tannate, 2 mg; pyrilamine tannate, 12.5 mg.

Description RYNATAN® is an antihistaminic/decongestant combination available for oral administration as *Tablets* and as *Pediatric Suspension*. Each tablet contains:

Phenylephrine Tannate	25 mg
Chlorpheniramine Tannate	8 mg
Pyrilamine Tannate	25 mg

Other ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, methylcellulose, polygalacturonic acid, talc.

Each 5 mL (teaspoonful) of the Pediatric Suspension contains:

Phenylephrine Tannate	5 mg
Chlorpheniramine Tannate	2 mg
Pyrilamine Tannate	12.5 mg

Other ingredients: benzoic acid, FD&C Red No. 3, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, sucrose.

Clinical Pharmacology RYNATAN combines the sympathomimetic decongestant effect of phenylephrine with the antihistaminic actions of chlorpheniramine and pyrilamine.

Indications and Usage RYNATAN is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications RYNATAN is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine oxidase (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery while using this product.

Drug interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, mutagenesis, impairment of fertility: No long term animal studies have been performed with RYNATAN®.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with RYNATAN. It is also not known whether RYNATAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RYNATAN should be given to a pregnant woman only if clearly needed.

Nursing mothers: RYNATAN should not be administered to a nursing woman.

Adverse Reactions Adverse effects associated with RYNATAN at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Overdosage *Signs and symptoms:* May vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment: Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration Administer the recommended dose every 12 hours.
RYNATAN Tablets: Adults — 1 or 2 tablets.
RYNATAN Pediatric Suspension: *Children over six years of age* — 5 to 10 mL (1 to 2 teaspoonfuls); *Children two to six years of age* — 2.5 to 5 mL (½ to 1 teaspoonful); *Children under two years of age* — Titrate dose individually.

How Supplied RYNATAN® Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and 500 (NDC 0037-0713-96).

RYNATAN® Pediatric Suspension: pink with strawberry-currant flavor, in 4 fl. oz. bottles (NDC 0037-0715-67, labeled RYNATAN®-S*) and in pint bottles (NDC 0037-0715-68).

Storage: RYNATAN® Tablets — Store at room temperature; avoid excessive heat — above 40°C (104°F).

RYNATAN® Pediatric Suspension — Store at controlled room temperature — between 15°C–30°C (59°F–86°F); protect from freezing.

**Patent Pending*

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Communicative Disorders **Facial Plastic & Reconstructive Surgery**

33

Segmental Mandibular Regeneration

Histotoxicity of Tissue Adhesives

Facial Bone Augmentation

Treatment in Chronic Otitis Media

Trends in Cochlear Implantation

Split-Palate Approach

Complications in CHARGE Association

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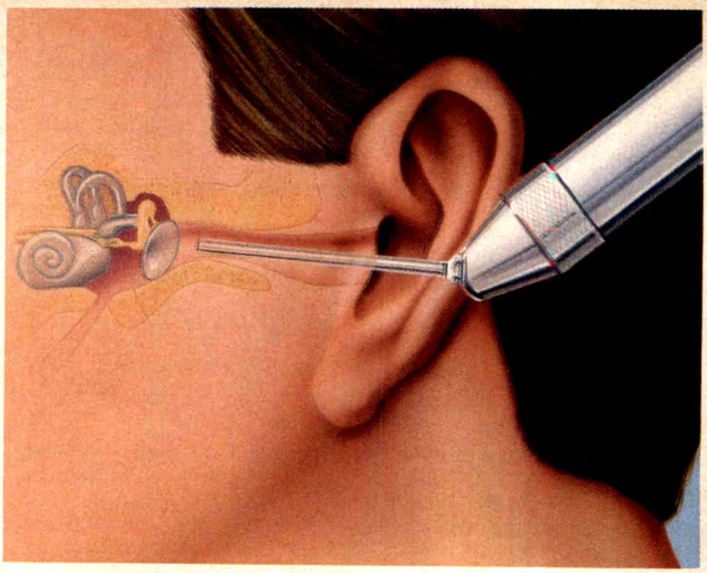

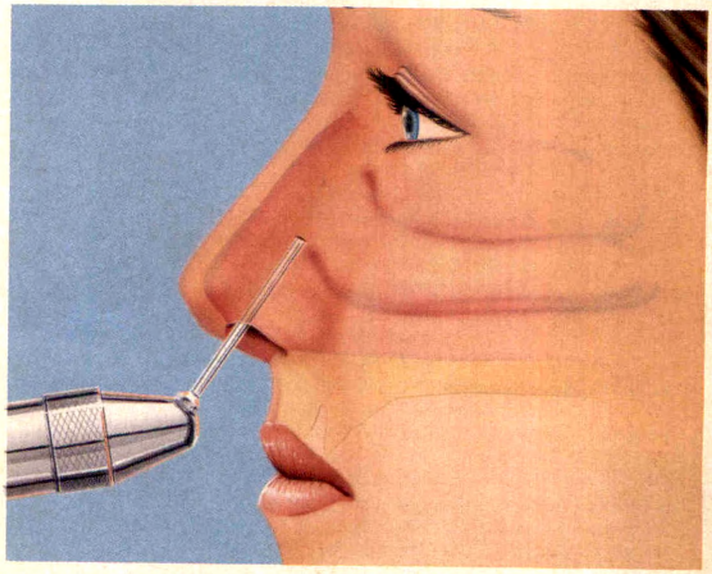

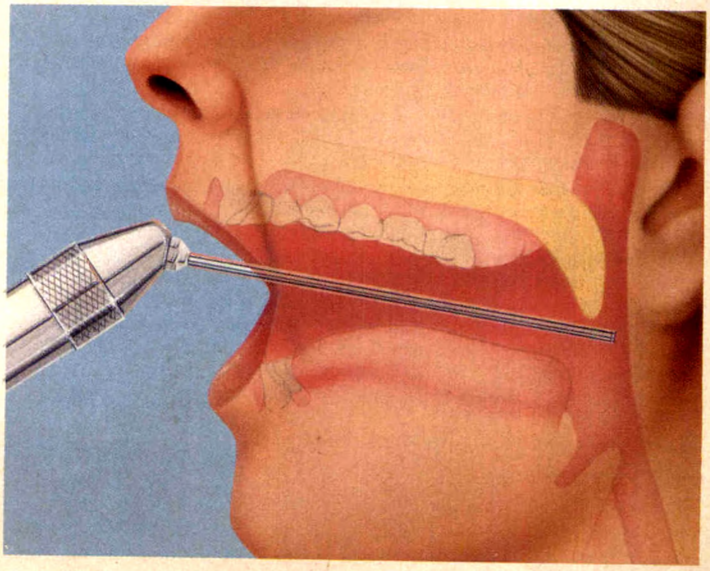

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for seasonal allergic rhinitis

Starts fast and lasts

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Seldane®

(terfenadine) 60 mg Tablets

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients: Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility: Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C. There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use: Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General: Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia, torsade de pointes and ventricular fibrillation), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of January, 1990 Y460D
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IMMUNOBIOLOGY: HEAD AND NECK CANCER 1990

September 21-22, 1990
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This interdisciplinary symposium is designed to generate basic science and clinical discussion among leaders in the field of tumor immunology in head and neck cancers. It coincides with recent major advances in immunology and with an increased understanding of the mechanisms of clinical immunosuppression and the potential for immunomodulation in these malignancies. The symposium will be of particular interest to specialists in otolaryngology, immunology, immunopathology, head and neck surgery, and oncology.

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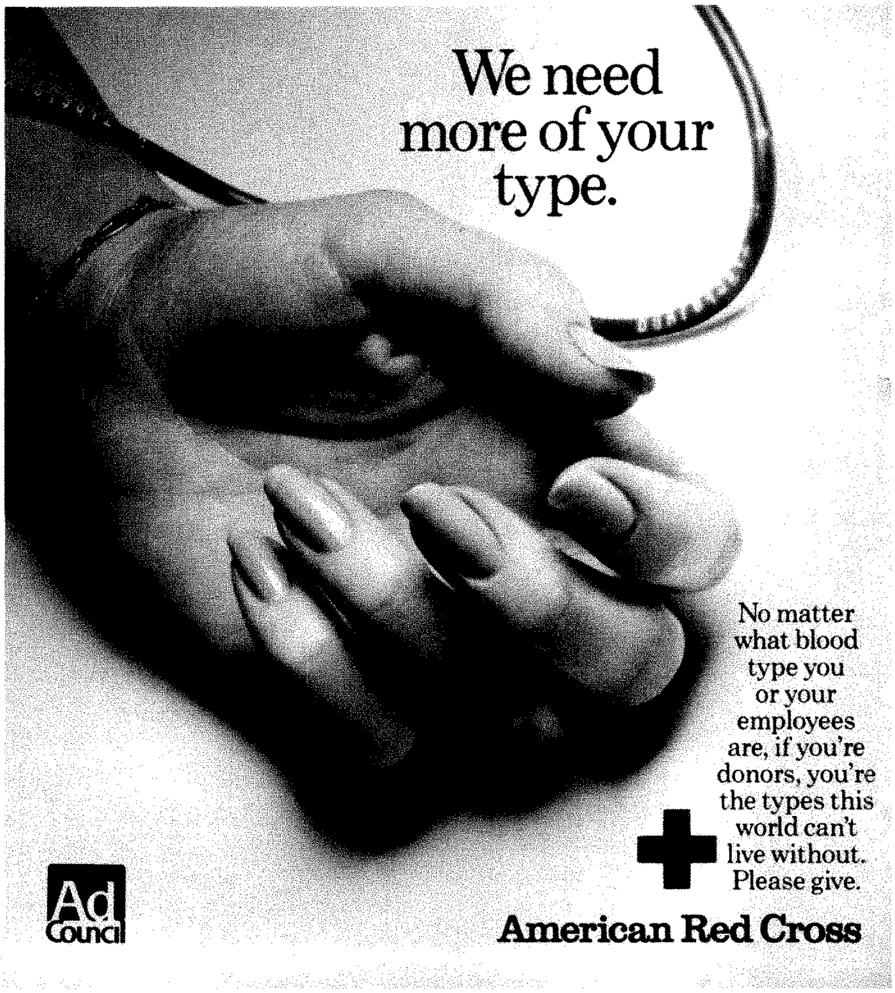
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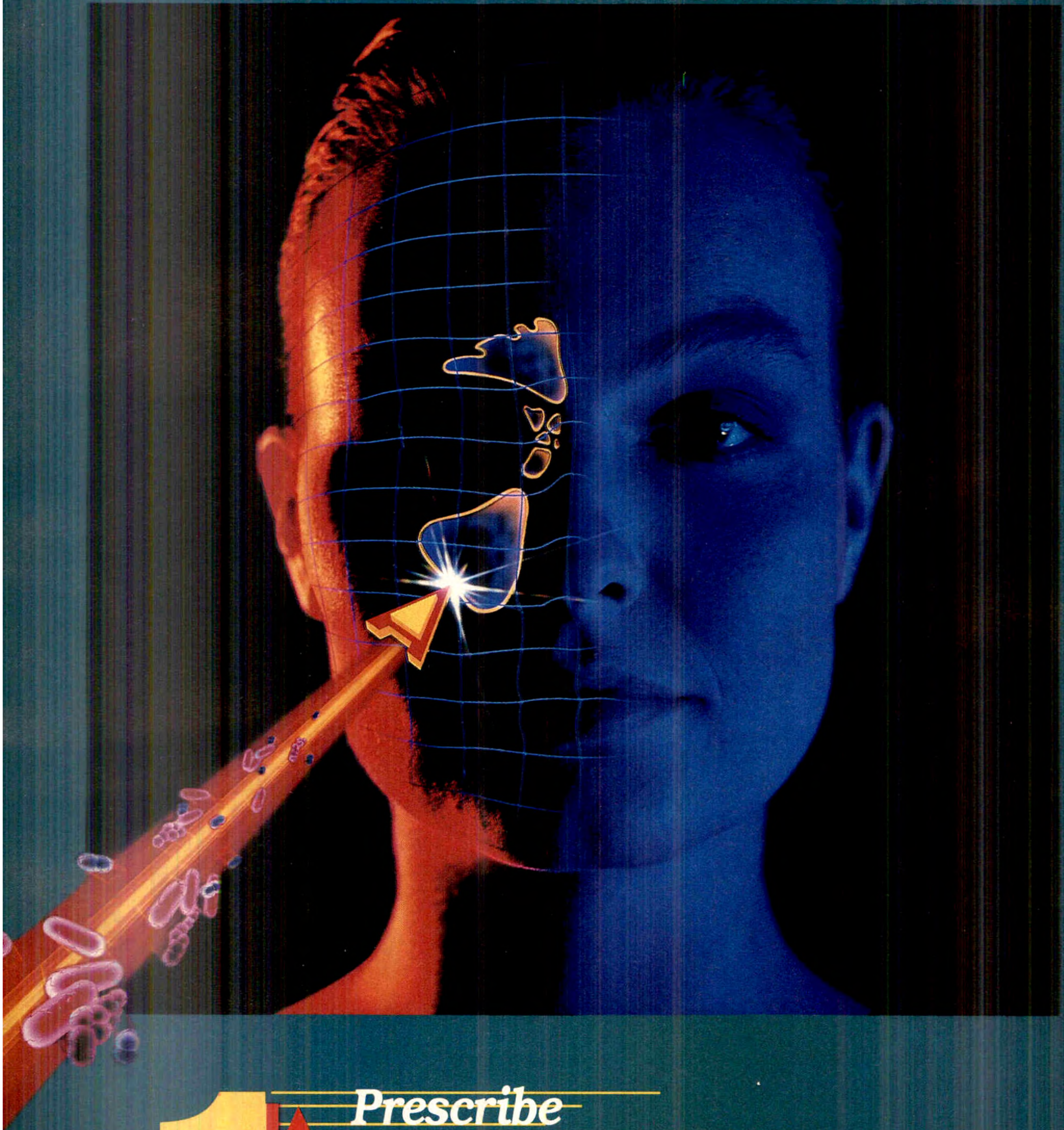

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amoxicillin/clavulanate potassium

First time, first-line for clinical certainty

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Please see brief summary of prescribing information on adjacent page.

Brief Summary of Prescribing Information

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Indications and Usage: AUGMENTIN® is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to AUGMENTIN treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to AUGMENTIN, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to AUGMENTIN when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While AUGMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN and allopurinol administered concurrently.

AUGMENTIN should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to AUGMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of AUGMENTIN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when AUGMENTIN is administered to a nursing woman.

Adverse Reactions: AUGMENTIN is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%), and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT and/or SGPT has been noted in patients treated with ampicillin class antibiotics as well as with AUGMENTIN, but the significance of these findings is unknown. As with some other penicillins, and some cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with AUGMENTIN.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one AUGMENTIN '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one AUGMENTIN '500' tablet every eight hours.

Since both the AUGMENTIN '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two AUGMENTIN '250' tablets are not equivalent to one AUGMENTIN '500' tablet. Therefore, two AUGMENTIN '250' tablets should not be substituted for one AUGMENTIN '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as AUGMENTIN '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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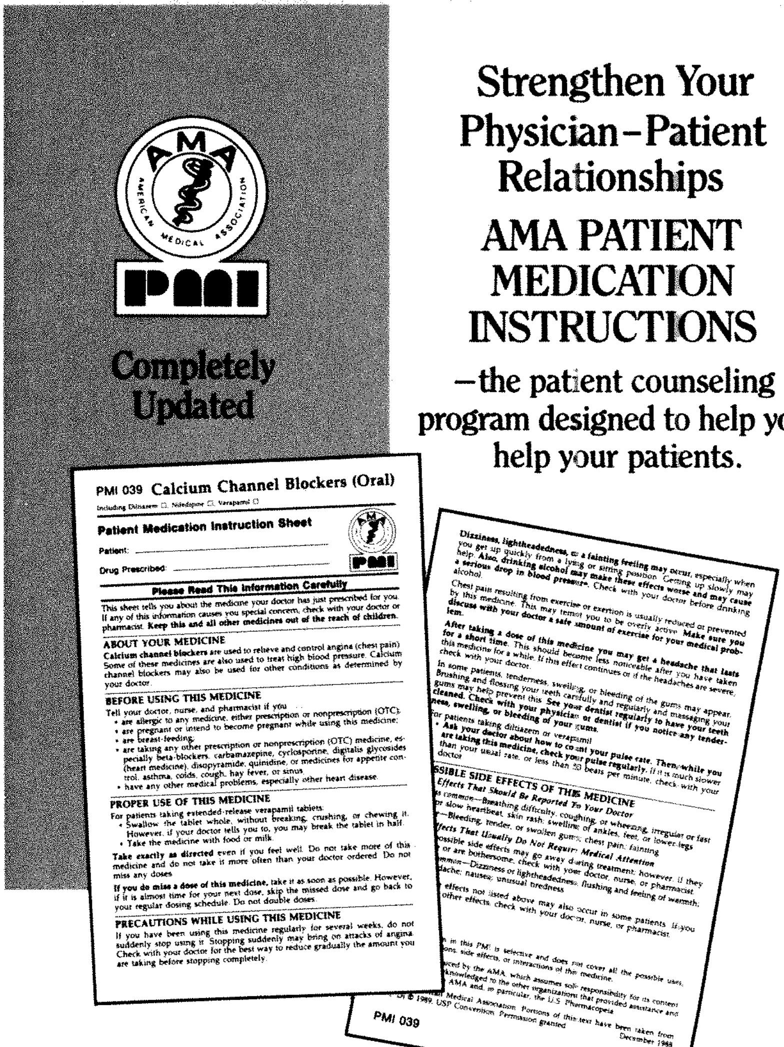

PMI 039 Calcium Channel Blockers (Oral)

Including Diltiazem ☐, Nifedipine ☐, Verapamil ☐

Patient Medication Instruction Sheet

Patient: ____________________

Drug Prescribed: ____________________

Please Read This Information Carefully

This sheet tells you about the medicine your doctor has just prescribed for you. If any of this information causes you special concern, check with your doctor or pharmacist. **Keep this and all other medicines out of the reach of children.**

ABOUT YOUR MEDICINE

Calcium channel blockers are used to relieve and control angina (chest pain). Some of these medicines are also used to treat high blood pressure. Calcium channel blockers may also be used for other conditions as determined by your doctor.

BEFORE USING THIS MEDICINE

Tell your doctor, nurse, and pharmacist if you . . .

- are allergic to any medicine, either prescription or nonprescription (OTC);
- are pregnant or intend to become pregnant while using this medicine;
- are breast-feeding;
- are taking any other prescription or nonprescription (OTC) medicine, especially beta-blockers, carbamazepine, cyclosporine, digitalis glycosides (heart medicine), disopyramide, quinidine, or medicines for appetite control, asthma, colds, cough, hay fever, or sinus.
- have any other medical problems, especially other heart disease.

PROPER USE OF THIS MEDICINE

For patients taking extended-release verapamil tablets:

- Swallow the tablet whole, without breaking, crushing, or chewing it. However, if your doctor tells you to, you may break the tablet in half.
- Take the medicine with food or milk.

Take exactly as directed even if you feel well. Do not take more of this medicine and do not take it more often than your doctor ordered. Do not miss any doses.

If you do miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

PRECAUTIONS WHILE USING THIS MEDICINE

If you have been using this medicine regularly for several weeks, do not suddenly stop using it. Stopping suddenly may bring on attacks of angina. Check with your doctor for the best way to reduce gradually the amount you are taking before stopping completely.

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Instructions for Authors

NOTE: *Please read these instructions carefully—technical deficiencies must be corrected before manuscripts can be reviewed.*

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Any manuscript, Letter to the Editor, or other material sent for publication must be accompanied by a letter containing the following language: "In consideration of the American Medical Association's taking action in reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the AMA in the event that such work is published by the AMA." We regret that transmittal letters not containing the foregoing language *signed by all authors* of the submission will necessitate delay in the review of the manuscript.

In case the work was done by a federal employee, each author must include a signed statement that the work reported was done while he or she was employed by the federal government.

Author Responsibility.—All accepted manuscripts are subject to copy editing. The author will receive an edited typescript and layout rather than galley or page proofs for approval. The author is responsible for all statements in his work, including changes made by the copy editor.

Title.—Titles should not exceed 75 characters, including punctuation and spaces.

Title Page (First Page).—The title page should include all authors' full names, highest degrees, academic affiliations, and, if the manuscript was presented at a meeting, the name of the meeting, the place it was held, and the date on which it was read. One author should be designated as corresponding author, with his or her name, address, and telephone number. Specify the address to which requests for reprints should be sent. Order reprints at the time the typescript is returned after editorial processing.

Abstract (Second Page).—Provide a double-spaced abstract (135-word maximum) of the article. Abstract should include statements of problem, method of study, results, and conclusions. Do not include a "summary" section in the main manuscript.

Manuscript Preparation.—Submit the original typed manuscript **plus** two high-quality copies of the entire manuscript. *The entire manuscript,* including abstract, references, legends, and tables, *must be typewritten, double-spaced,* on 21.6 × 27.9-cm (8½ × 11-in) heavy-duty white bond paper. Ample margins of at least 2.5 cm (1 in) should be provided. Do not justify the right margin if a word processor is used.

SI Units.—Use Système International (SI) measurements throughout the manuscript.

References.—List references, double-spaced, in consecutive numerical order (the order of citation in the manuscript, not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications will not be accepted as references. References to journal articles should include (1) authors (list all authors and/or editors up to six; if more than six, list the first three and "et al"), (2) title, (3) journal name (as abbreviated in *Index Medicus*), (4) year, (5) volume number, and (6) inclusive page numbers, in that order. References to books should include (1) authors (list all authors and/or editors up to six; if more than six, list the first three and "et al"), (2) chapter title (if any), (3) editors (if any), (4) title of book, (5) city of publication, (6) publisher, and (7) year. Volume and edition numbers, specific pages, and name of translator should be included when appropriate. **The author is responsible for the accuracy and completeness of the references and for their correct text citation.** Please note this journal's punctuation and sequence style preference in previously published reference listings.

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Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 21.6 × 27.9-cm (8½ × 11-in paper. Do not use larger paper. If a table must be continued, use a second sheet and repeat all heads and stubs.

Consent Forms.—Manuscripts reporting the results of experimental investigations of human subjects must include a statement to the effect that informed consent was obtained after the nature of the procedure(s) had been fully explained.

A letter of consent must accompany all photographs of patients in which a possibility of identification exists. It is no longer sufficient to cover the eyes to mask identity. If a photograph is of a minor, then *both parents must sign* the consent form.

Refer to patients by number (or, in anecdotal reports, by fictitious given names). Real names or initials should not be used in the text, tables, or illustrations.

Illustrations.—Submit illustrations in duplicate, unmounted, untrimmed, and 12.7 × 17.3 cm (5 × 7 in). Send high-contrast glossy prints (not photocopies). Figure number, name of senior author, and arrow indicating "top" should be typed on a gummed label and affixed to the back of the illustration.

Illustrations in full color are accepted for publication if the editors believe that color will add significantly to the published manuscript. The ARCHIVES will pay part of the expense of reproduction and printing color illustrations, the remainder to be borne by the author or his sponsor. After deducting the ARCHIVES' contribution, the author's share is $400 for up to six square-finished illustrations that can be arranged on a one-page layout. Any additional illustrations or special effects will be billed to the author at cost. Positive color transparencies (35 mm preferred) must be submitted for an evaluation. Do not send color prints unless accompanied by original transparencies. Do not submit glass-mounted transparencies.

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____ (2) Failure to double-space entire manuscript (abstract, references, legends, and tables).

____ (3) Failure to convert to SI units.

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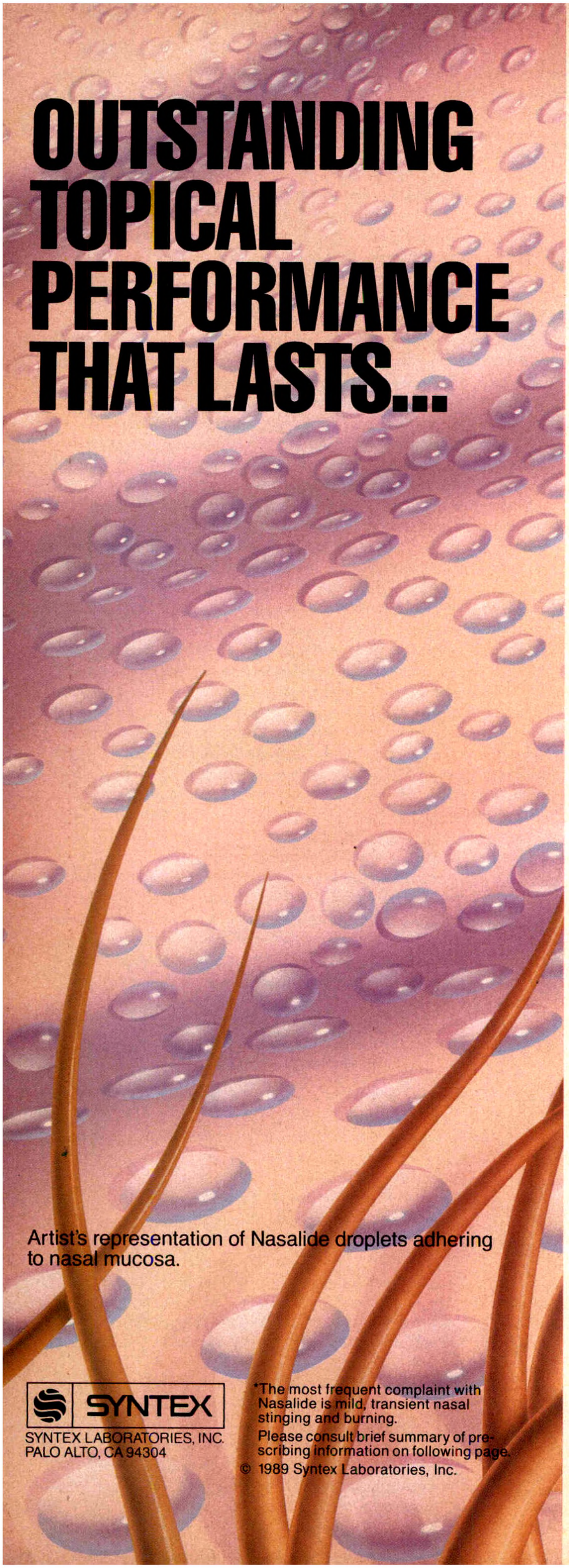

Artist's representation of Nasalide droplets adhering to nasal mucosa.

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*The most frequent complaint with Nasalide is mild, transient nasal stinging and burning.

Please consult brief summary of prescribing information on following page.

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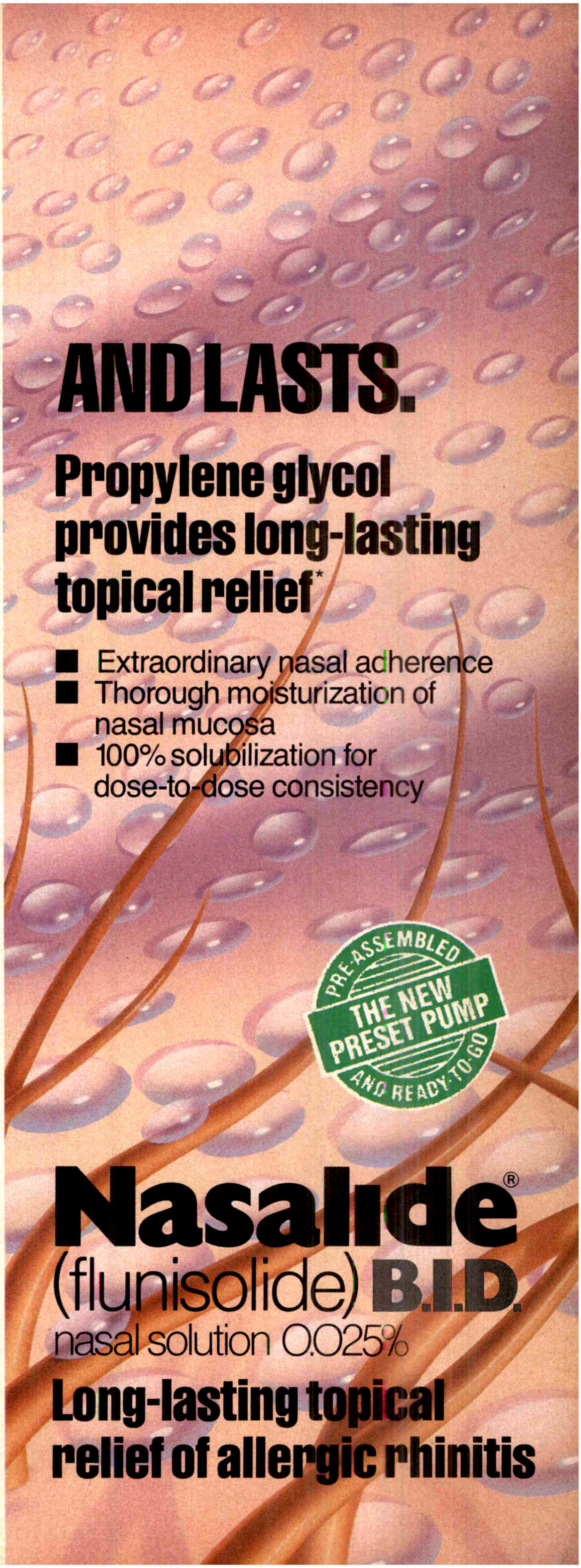

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- 100% solubilization for dose-to-dose consistency

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(flunisolide) **B.I.D.**
nasal solution 0.025%

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Nasalide® B.I.D.
(flunisolide) nasal solution 0.025%

Brief Summary

Description: Each bottle of NASALIDE® (flunisolide) nasal solution contains flunisolide in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water, with NaOH and/or HCl added to adjust the pH. It contains no fluorocarbons.

Indications: For topical treatment of the symptoms of seasonal or perennial rhinitis when effectiveness of or tolerance to conventional treatment is unsatisfactory.

Improvement is based on a local effect rather than systemic absorption. Improvement is usually apparent within a few days after starting Nasalide but may take as long as 2 weeks in some patients. Although systemic effects are minimal at recommended doses, Nasalide should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. Nasalide should not be used in the presence of untreated localized infection involving nasal mucosa.

Contraindications: Hypersensitivity to any ingredients.

Warnings: Patients transferred from systemic steroid therapy to Nasalide should be monitored to avoid acute adrenal insufficiency in response to stress. Since some patients may experience symptoms of withdrawal, attention must be given to patients previously treated for prolonged periods with systemic corticosteroids, particularly those with associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of symptoms. Nasalide should be used with caution in patients on alternate-day prednisone for any disease.

Precautions: General: Localized *Candida albicans* infections of the nose and pharynx occurred only rarely in clinical studies, but if such an infection presents, treatment with appropriate local therapy or discontinuation of Nasalide treatment may be required.

Flunisolide is absorbed into the circulation. Systemic effects have been minimal with recommended doses but larger doses should be avoided since excessive doses may suppress hypothalamic-pituitary-adrenal function.

Nasalide should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

In patients who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery, or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Information for Patients: Nasalide should be used as directed at the prescribed dosage. Nasal vasoconstrictors or oral antihistamines may be needed until the effects of Nasalide are fully manifested. The patient should follow the Patient Instructions carefully and should contact a physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs.

Carcinogenesis: Long-term studies showed a slight increase in the incidence of pulmonary adenomas in mice, but not in rats.

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids.

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in low and mid-dose groups was comparable to controls.

Pregnancy: Pregnancy Category C. The drug has been shown to be teratogenic and fetotoxic in rabbits and rats. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because other corticosteroids are excreted in human milk, caution should be exercised when the drug is administered to nursing women.

Adverse Reactions: The most frequent complaints were mild transient nasal burning and stinging (reported in approximately 45% of patients). These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of these symptoms.

Incidence of 5% or less: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headaches and loss of sense of smell and taste. As is the case with other nasally inhaled corticosteroids, nasal septal perforations have been observed in rare instances.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism could occur.

Dosage and Administration: Full therapeutic benefit requires regular use and is usually evident within a few days, but up to 3 weeks may be required for some patients to achieve maximum benefit. Patients should use a decongestant and clear their nasal passages of secretions prior to use. Recommended starting dose in adults: 2 sprays in each nostril b.i.d. If needed, increase to 2 sprays t.i.d.

Recommended starting dose in children (6-14 years): 1 spray in each nostril t.i.d. or 2 sprays in each nostril b.i.d. Not recommended for use in children less than 6 years old.

Total daily doses: not to exceed 8 sprays in each nostril for adults and 4 sprays in each nostril for children.

Maintenance dose: smallest amount necessary to control symptoms.

How Supplied: Each 25 ml Nasalide® (flunisolide) nasal solution spray bottle (NDC 0033-2906-40) (NSN 6505-01-132-9979) contains 6.25 mg (0.25 mg/ml) of flunisolide and is supplied with a nasal pump unit with dust cover, and patient instructions.

Rev. July 1989

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- recommendation of policy to the House of Delegates on Prioritization of Health Care Expenditures and Notification of Denials by the PRO;
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HMSS

Facial Plastic News

WAYNE F. LARRABEE, MD, SECTION EDITOR
Virginia Mason Clinic, Seattle, Wash

New Techniques in Surgery of the Aging Face

Various new areas of aesthetic surgery were discussed at the Fifth International Symposium in Toronto. Dr Jacques Faivre and John-Marie Faivre, Paris, France, presented a series of over 300 patients who underwent cosmetic surgical correction of thin and wrinkled lips. Long-term results (5 years) were presented that generated a tremendous amount of interest. Their technique involved harvesting de-epithelialized dermis from the suprapubic area and implanting it through intraoral stab incisions. The length of the lip was measured and a dermal graft approximately 1-cm wide, tapered at each end, and slightly longer than the length of the measurement of the lip was harvested. Through a stab incision made intraorally at the commissure, a Kelly clamp was placed *within* the orbicularis oris muscle and gently threaded to the opposite commissure. A stab incision was made and then the dermal fat graft with a small amount of fat on the back side of this graft was pulled back through the orbicularis oris muscle. Their results showed the elimination of many of the atrophic vertical lines that develop with aging and the creation of a more permanent full-bodied lip.

Other adjunctive procedures that created considerable interest were the silicone implants to the facial skeleton. Dr George Brennan, Newport Beach, Calif, presented his work on temporal augmentation using a custom-made silicone implant placed under the temporalis fascia in the temporal fossa to correct the sunken appearance above the zygomatic arch and behind the superior lateral orbital rim. In addition, he showed the results of forehead augmentation using a subperiosteal silicone graft that lay in the forehead to create a full rounded appearance instead of a concavity. Dr William Binder, Los Angeles, Calif, presented his technique on submalar augmentation. Due to absorption of the bony skeleton along with the gravitational pull of the cheek soft tissues inferiorly, a groove develops that creates a sad looking face with poor malar projection. Dr Binder showed a videotape of his intraoral approach in which a pocket is created that runs from the infraorbital nerve laterally under the malar eminence to extend under the zygomatic arch where the implant sits. He then secures it with a suture through the cheek tied over a batten to make sure it stays in position. Dr Binder, Dr Brennan, and many other surgeons at the conference felt that skeletal augmentation, particularly cheek augmentation, is an integral part of facial rejuvenation.

Dr Marcello Hochman, Mountain View, Calif, and Dr Brennan discussed the use of Tutoplast for the augmentation of the dorsum in rhinoplasty. Tutoplast is lyophilized human dura that can be placed in layers and held securely with Histocryl.

Dr Arif Shaikh discussed his use of acrylic glue in facial plastic surgery; skin approximation in preauricular incisions using Histocryl after an adequate subcutaneous closure resulted in excellent epithelial reapproximation. However, Dr Ellis, who coauthored the paper stated that his experimental studies have shown that Histocryl produces a reaction when implanted subcutaneously. Its use in reapproximating the epithelium has been widespread in Canada.

Dr Pierre Giamnanco, Bloomfield Hills, Mich, presented his experimental clinical work using initially Supramed mesh and then Gortex as a sling to augment the results of liposuction in the cervical area. This graft was placed with the suction cannula and has held up quite nicely. He was careful to point out that this is not an accepted procedure and is still in the experimental stage, but the results he achieved make the cervicomental angle more acute and deserve careful observation.

FACE AND CERVICAL LIFT TECHNIQUES

The search for a long lasting and adequate cosmetic result in the anterior cervical area continues to be explored. More and more surgeons are coming to the realization that anterior cervical banding can only be corrected by some sort of direct manipulation. Dr Larry Lefkoff, Los Angeles, Calif, and Dr Frank Kamer, Beverly Hills, Calif, presented their graduated approach to a difficult problem in which they showed a four-level classification of the face that required tailoring the face-lift procedure to the particular class and pathologic defect. This was reiterated when Dr Kamer presented his 20-year experience in rhytidectomy, stressing the fact that flexibility, honesty, and the need to tailor the operation and adjust to new techniques must be incorporated into one's practice. Dr Kamer, for the past 3 years, has sutured the platysma bands together in the midline after making a short horizontal cut in the band in the neck. Posteriorly he continues to advocate a sub-SMAS—platysma flap as the preferred means for rebuilding the foundation of the face. This flap is secured with multiple 3-0 Dexon sutures. He has found that the use of permanent buried sutures tends to cause more problems than they solve, especially years later when they can be extruded and/or produce granulomas.

A panel moderated by Dr Bill Benson, Indianapolis, Ind, discussed the management of the submental and cervical tissues. Dr Ivo Pitangui, Brazil, presented the modification of the SMAS and platysma work that he has been doing over the years. Dr Gaylon McCullough cautioned that undermining and subcutaneous manipulation must be done judiciously and not to the extent that results are less and the risk of postoperative complications increase. Dr Brennan showed his technique for correction of the witch's chin or ptotic chin by mobilizing the subcutaneous layer of fat and suturing it above the chin to increase the chin protrusion, elevate the ptotic chin, and smooth out the redundant skin that is so common in the witch's or ptotic chin deformity. Dr Beeson presented his work, which involved the extended cervical undermining posteriorly, along with mobilization of the SMAS platysma complex. By suturing the posterior border of the platysma muscle posteriorly over the occipital area and redraping these long flaps, one can correct the laxity of the submental area and achieve adequate redraping of the skin and the face-lift procedure.

Dr Guy Jost, Paris, France, reviewed the surgical anatomy of the fascia in the facelift; he feels there is no real SMAS layer, but instead what we are calling the SMAS is fibrous platysma. He stated that the platysma muscle was the only muscle in the body that did not insert into bone but instead into the parotid gland and fascia itself. From his illustrations it was evident that one could dissect on top of the parotid (beneath this fibrous platysma-fascia layer) and avoid injury to the facial nerve as it exited the gland anteriorly. He further showed that elevating a large fascial fibrous platysma muscle layer below the zygomatic arch and redraping it, one could obtain a suitable reconstruction of the foundation of the face and thereby improve not only the postoperative results, but the length of time that it lasted. Tony Bull, London, England, reviewed the alar cartilage anatomy and cautioned against dividing the dome when the cephalic border of the lateral crus is excised. By avoiding the dome area, postoperative knuckling and other irregularities could be avoided. However, should these knuckles and sequelae develop postoperatively, they can be corrected with free cartilage onlay grafts.

Dr George Toledo, Dallas, Tex, reviewed the coronal approach for rejuvenation of the upper third of the face. He routinely closes the galae to take tension off the scalp closure to avoid wound separation and alopecia. He also felt that electrocautery and clamping of hair follicles could precipitate hair loss. Dr Toledo presented the orbicularis oculi plication technique for correcting crows feet and felt that while this was adequate in some cases, chemical peel was still probably the method of choice for this problem.

Dr Faivre, Paris, France, presented probably the most exciting and controversial technique on the aging face when he presented his deep temporal facelift. In effect, this is the subperiosteal facelift that has been discussed recently by others. He divided patients into three categories. The one category of patients required only a temporal lift, and by dissecting the periosteum of the orbital rim from the supraorbital nerve laterally around the orbit to the inferior orbital rim and zygomatic arch, the deep structures could be elevated and secured with multiple permanent sutures. This, in effect, elevated the eyebrow and the corner of the eye, producing an improvement analogous to the coronal lift. Interestingly, no scalp or skin was excised in this procedure. The second category of patient was one in which the dissection extended underneath the orbital rim down the anterior maxilla to elevate the deep structures of the malar area, thereby reducing the line of the cheek lip fold. Again, no scalp or skin was excised and suspension sutures were placed. The third category of patient was one in which the temporal and middle aspect of the face were elevated through the subperiosteal approach and a regular cervical facial rhytidectomy was carried out in a different plant. This new technique clearly needs careful clinical study and evaluation to judge its safety and usefulness.

—DOUGLAS D. DEDO, MD, West Palm Beach, Fla

IN OTHER AMA JOURNALS

ARCHIVES OF OPHTHALMOLOGY

Senate Bill Passed Too Late to Avoid Automatic Funding Cuts
Julie Foreman (*Arch Ophthalmol.* 1989;107:1729)

The Interaction Between Ophthalmology and Society: History Suggests Strategy
Joel G. Sacks, MD, MBA (*Arch Ophthalmol.* 1989;107:1740-1742)

JAMA

Multivitamin/Folic Acid Supplementation in Early Pregnancy Reduces the Prevalence of Neural Tube Defects
A. Milunsky; H. Hick; S. S. Jick; C. L. Bruell; D. S. MacLaughlin; K. J. Rothman; W. Willett (*JAMA.* 1989;262:2847)

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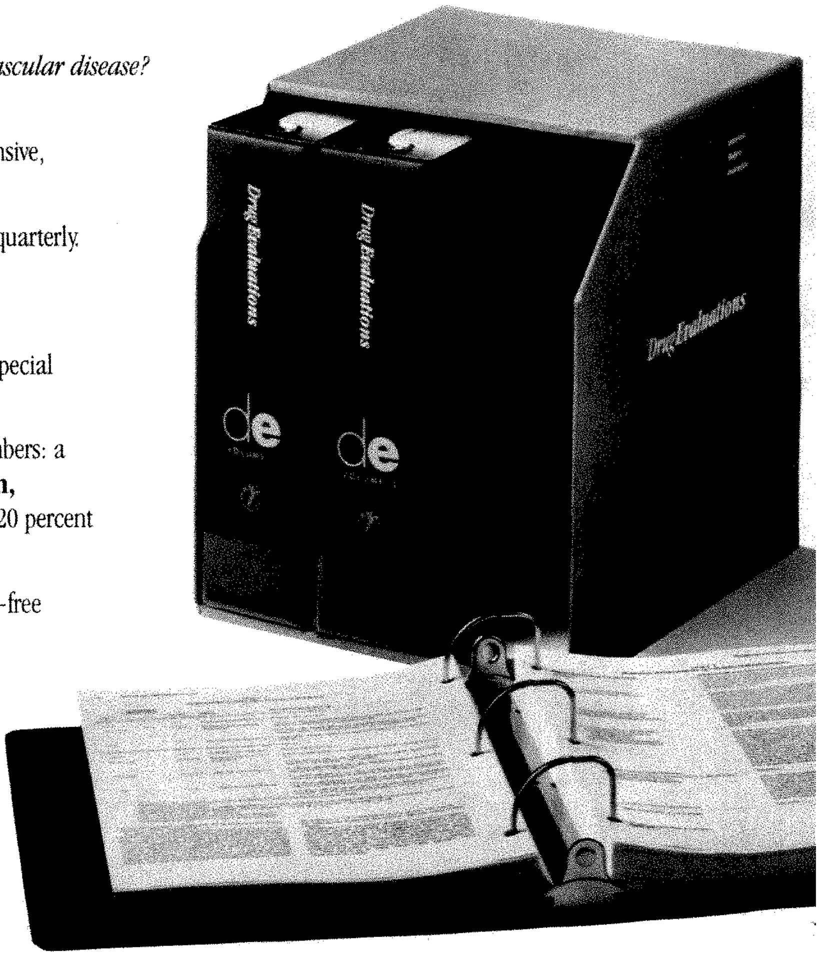

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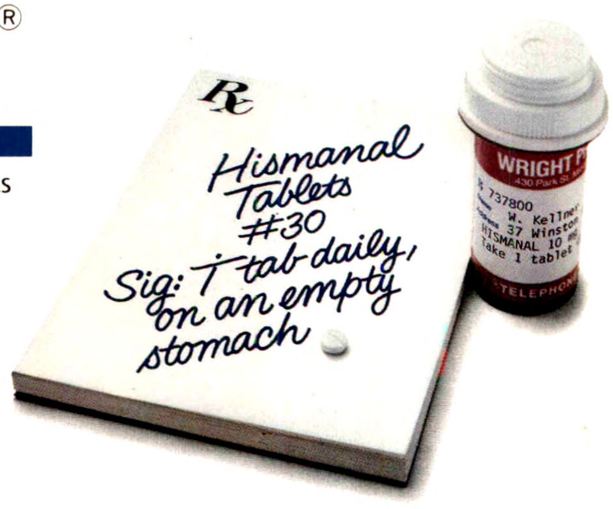

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Caution should be used in patients with cirrhosis or other liver diseases (See Clinical Pharmacology section).

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Information for Patients: Patients taking HISMANAL should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting HISMANAL therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby (see Pregnancy subsection). Patients should be instructed 1) to take HISMANAL only as needed, 2) not to exceed the prescribed dose, and 3) to take HISMANAL on an empty stomach, e.g., at least 2 hours after a meal. No additional food should be taken for at least 1 hour post-dosing. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic potential has not been revealed in rats given 260x the recommended human dose of astemizole for 24 months, or in mice given 400x the recommended human dose for 18 months. Micronucleus, dominant lethal, sister chromatid exchange and Ames tests of astemizole have not revealed mutagenic activity.

Impairment of fertility was not observed in male or female rats given 200x the recommended human dose.

Pregnancy: Pregnancy Category C: Teratogenic effects were not observed in rats administered 200x the recommended human dose or in rabbits given 200x the recommended human dose. Maternal toxicity was seen in rabbits administered 200x the recommended human dose. Embryocidal effects accompanied by maternal toxicity were observed at 100x the recommended human dose in rats. Embryotoxicity or maternal toxicity was not observed in rats or rabbits administered 50x the recommended human dose. There are no adequate and well controlled studies in pregnant women. HISMANAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Metabolites may remain in the body for as long as 4 months after the end of dosing, calculated on the basis of 6 times the terminal half-life (See Clinical Pharmacology section).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because certain drugs are known to be excreted in human milk, caution should be exercised when HISMANAL is administered to a nursing woman. HISMANAL is excreted in the milk of dogs.

Pediatric Use: Safety and efficacy in children under 12 years of age has not been demonstrated.

ADVERSE REACTIONS

The reported incidences of adverse reactions listed in the following table are derived from controlled clinical studies in adults. In these studies the usual maintenance dose of HISMANAL® (astemizole) was 10 mg once daily.

	Percent of Patients Reporting		
	Controlled Studies*		
ADVERSE EVENT	Hismanal (N = 1630) %	Placebo (N = 1109) %	Classical** (N = 304) %
Central Nervous System			
Drowsiness	7.1	6.4	22.0
Headache	6.7	9.2	3.3
Fatigue	4.2	1.6	11.8
Appetite increase	3.9	1.4	0.0
Weight increase	3.6	0.7	1.0
Nervousness	2.1	1.2	0.3
Dizzy	2.0	1.8	1.0
Gastrointestinal System			
Nausea	2.5	2.9	1.3
Diarrhea	1.8	2.0	0.7
Abdominal pain	1.4	1.2	0.7
Eye, Ear, Nose, and Throat			
Mouth dry	5.2	3.8	7.9
Pharyngitis	1.7	2.3	0.3
Conjunctivitis	1.2	1.2	0.7
Other			
Arthralgia	1.2	1.6	0.0

*Duration of treatment in Controlled Studies ranged from 7 to 182 Days

**Classical Drugs: Clemastine (N = 137); Chlorpheniramine (N = 100); Pheniramine Maleate (N = 47); d-Chlorpheniramine (N = 20)

Adverse reaction information has been obtained from more than 7500 patients in all clinical trials. Weight gain has been reported in 3.6% of astemizole treated patients involved in controlled studies, with an average treatment duration of 53 days. In 46 of the 59 patients for whom actual weight gain data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported in clinical trials or spontaneously from marketing experience with HISMANAL include: angioedema, bronchospasm, depression, edema, epistaxis, myalgia, palpitation, photosensitivity, pruritus, and rash.

Marketing experiences include isolated cases of convulsions. A causal relationship with HISMANAL has not been established.

OVERDOSAGE

In the event of overdosage, supportive measures including gastric lavage and emesis should be employed. Cases of overdose have been reported from foreign marketing experience. Although overdoses of up to 500 mg have been reported with no ill effects, cases of serious ventricular arrhythmias, including Torsades de pointes, following overdoses of greater than 200 mg have been reported. Patients should be carefully observed and ECG monitoring is recommended in cases of suspected overdose. An appropriate antiarrhythmic treatment may be needed. HISMANAL does not appear to be dialyzable.

Care should be taken not to exceed dosing recommended in the DOSAGE AND ADMINISTRATION section.

Oral LD_{50} values for HISMANAL were 2052 mg/kg in mice and 3154 mg/kg in rats. In neonatal rats, the oral LD_{50} was 905 mg/kg in males and 1235 mg/kg in females.

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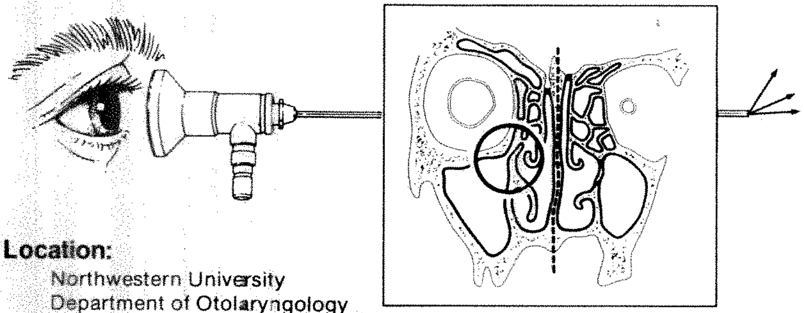

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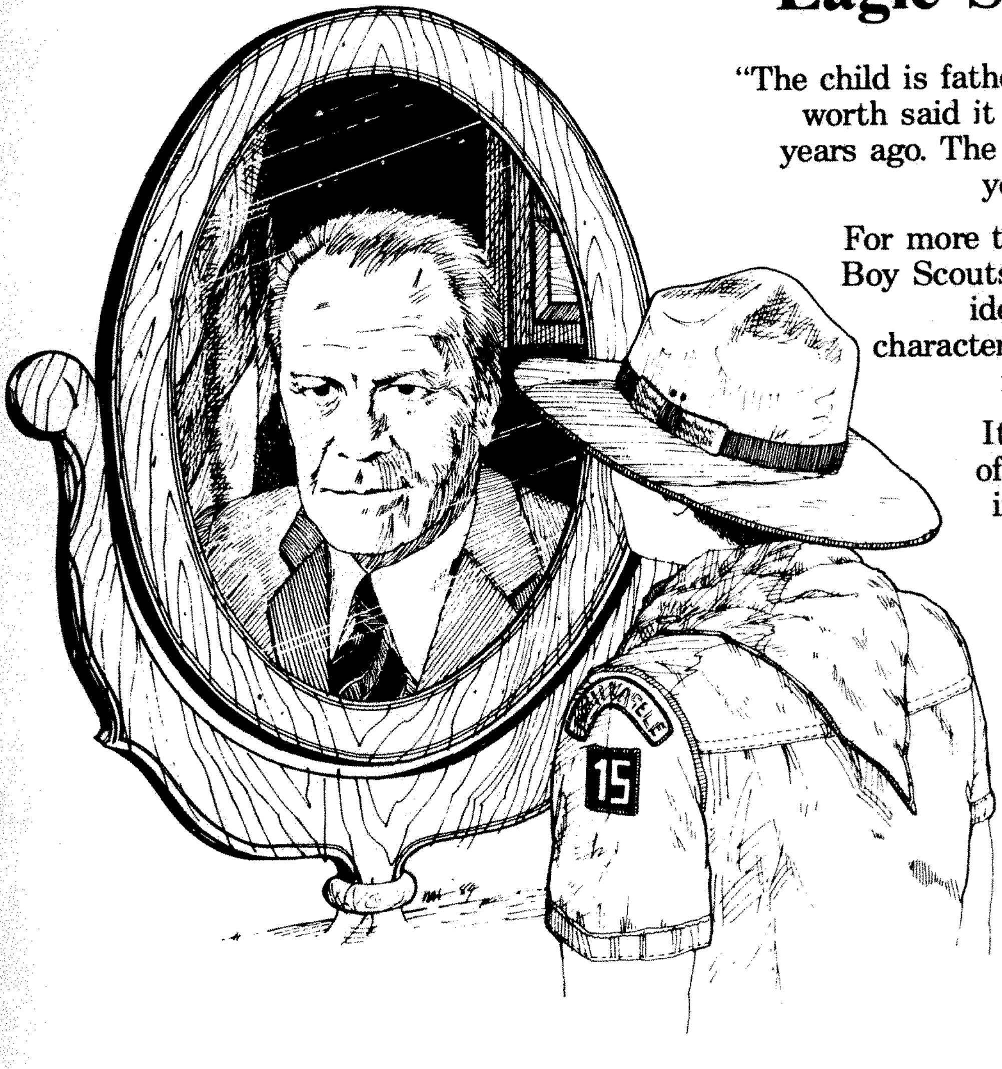

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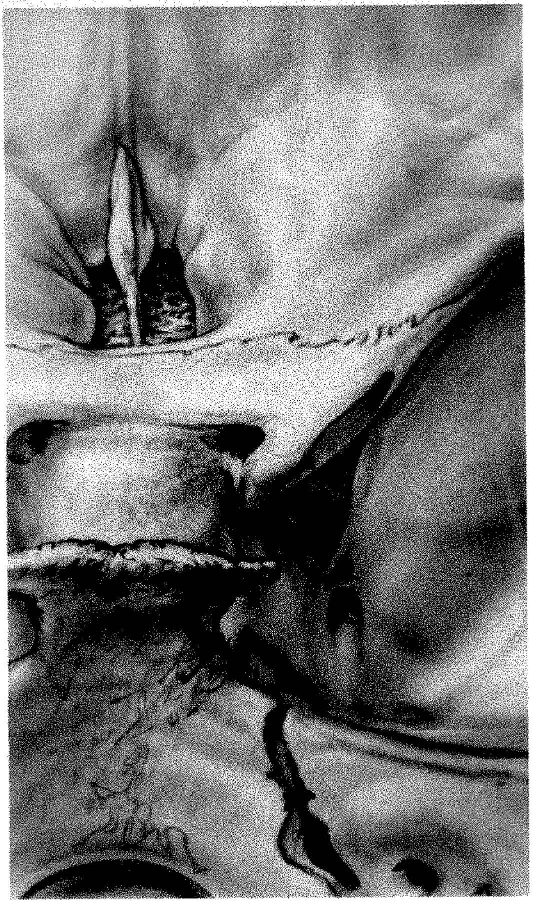

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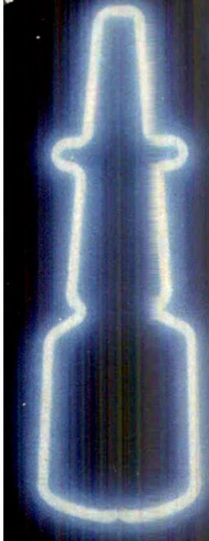

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Please see brief summary of prescribing information and references on following page.

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VP-148/16385506

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VANCENASE® AQ

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Nasal Spray 0.042%*

FOR INTRANASAL USE ONLY

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INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

Schering Corporation
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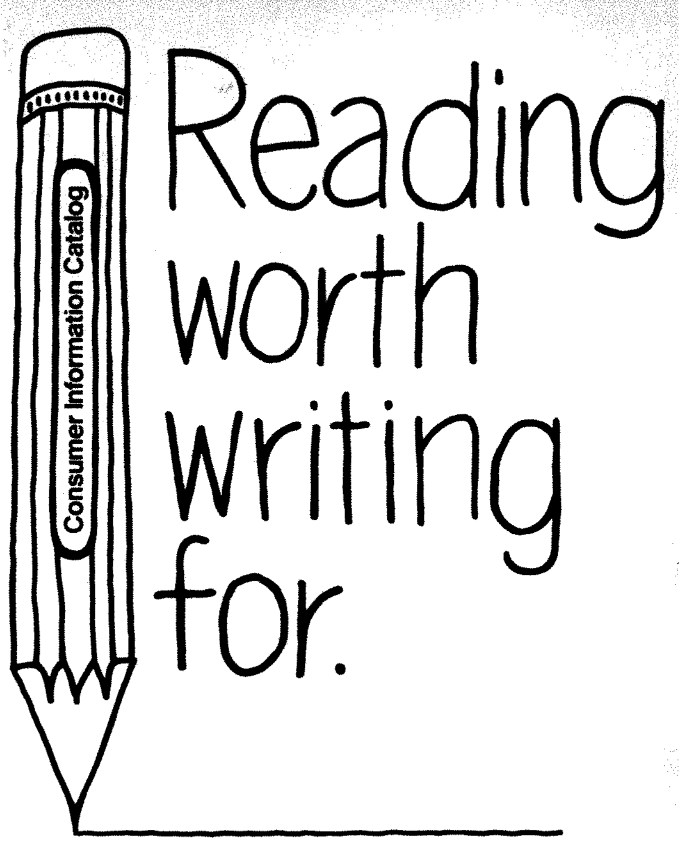

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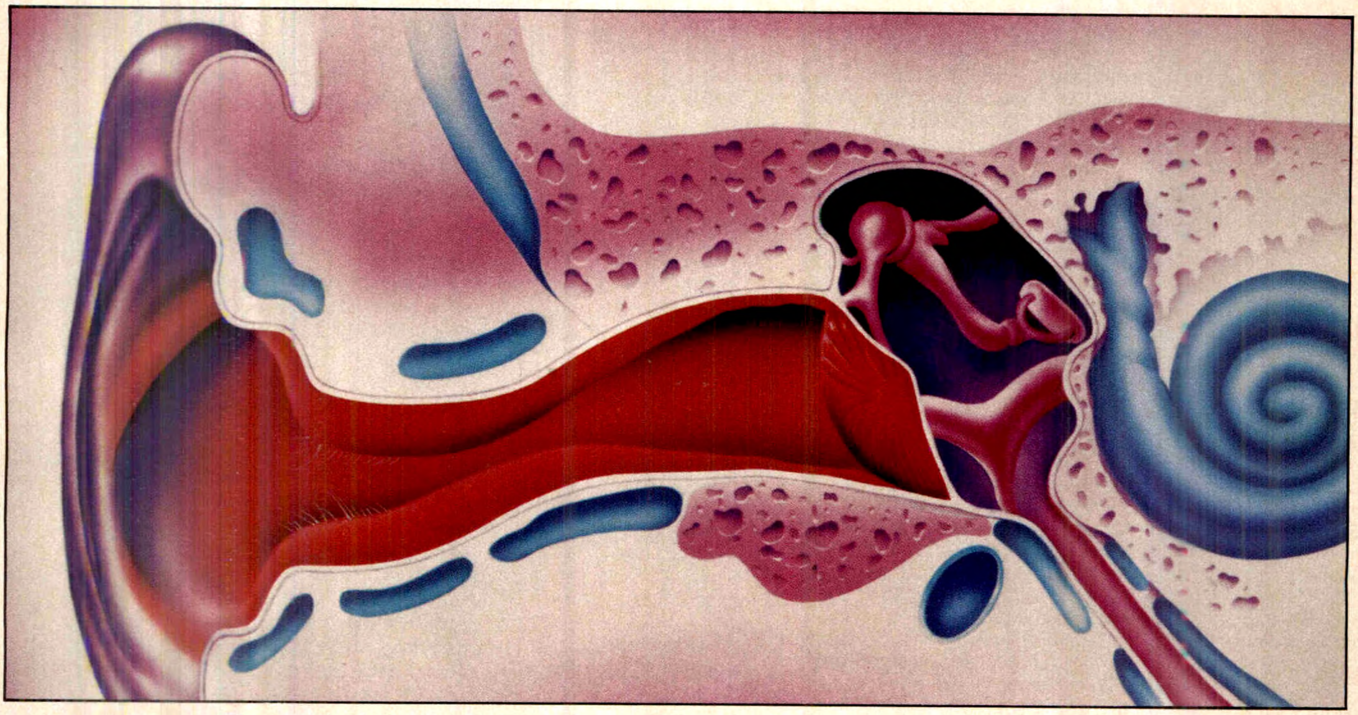

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*No resistant strains of susceptible organisms have been reported in vitro. (Does not necessarily imply a correlation with clinical results.)

References: 1. Ordonez GE, Kime CE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: I. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-polymyxin B otic solutions. *Curr Ther Res.* 1978;23(May suppl):SS3-SS14.
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3. Glassman JM, Pillar J, Soyka JP. Otitis externa: comparative *in vitro* sensitivities of clinical isolates of bacteria and fungi to nonantibiotic and antibiotic otic preparations. *Curr Ther Res.* 1978;23(May suppl):SS29-SS38.

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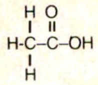
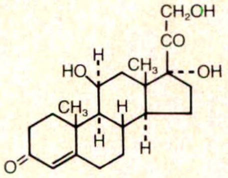
VōSoL HC (hydrocortisone and acetic acid otic solution, USP) also contains hydrocortisone (1%) and citric acid (0.05%). The empirical formulas for acetic acid and hydrocortisone are CH_3COOH and $C_{21}H_{30}O_5$, with a molecular weight of 60.05 and 362.46, respectively. The structural formulas are:



Acetic Acid



Chemically, hydrocortisone is:
Pregn-4-ene-3,20-dione,
11,17,21-trihydroxy-,(11β)-.

VōSoL and VōSoL HC are available as nonaqueous otic solutions buffered at pH 3 for use in the external ear canal.
Clinical Pharmacology: Acetic acid is anti-bacterial and anti-fungal; propylene glycol is hydrophilic and provides a low surface tension; benzethonium chloride is a surface active agent that promotes contact of the solution with tissues; hydrocortisone (in VōSoL HC) is anti-inflammatory, anti-allergic and anti-pruritic.
Indications and Usage: VōSoL—For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial.
VōSoL HC—For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation.
Contraindications: Hypersensitivity to any of the ingredients. VōSoL HC is contraindicated in vaccinia and varicella. Perforated tympanic membrane is considered a contraindication to the use of any medication in the external ear canal.
Warnings: Discontinue promptly if sensitization or irritation occurs.
Precautions: Transient stinging or burning may be noted occasionally when the solution is first instilled into the acutely inflamed ear.
Adverse Reactions: Stinging or burning may be noted occasionally; local irritation has occurred very rarely.
Dosage and Administration: Carefully remove all cerumen and debris to allow VōSoL to contact infected surfaces directly. To promote continuous contact, insert a wick saturated with VōSoL or VōSoL HC into the ear canal; the wick may also be saturated after insertion. Instruct the patient to keep the wick in for at least 24 hours and to keep it moist by adding 3 to 5 drops of VōSoL or VōSoL HC every 4 to 6 hours. The wick may be removed after 24 hours but the patient should continue to instill 5 drops of VōSoL 3 or 4 times daily thereafter, for as long as indicated.
How Supplied: VōSoL Otic Solution, in 15 mL (NDC 0037-3611-10) and 30 mL (NDC 0037-3611-30) measured-drop, safety-tip plastic bottles.
VōSoL HC Otic Solution, in 10 mL measured-drop, safety-tip plastic bottle (NDC 0037-3811-12).
Storage: Store at room temperature; avoid excessive heat. Keep container tightly closed. Rev. 5/89

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Fragmentation Within Otolaryngology-Head and Neck Surgery

Recent essays by prominent surgical leaders[1-5] have drawn attention to the phenomenon of specialization in medicine. Along with other major categories of change (technology, education, economic, political), one impact of specialization is its tendency to rearrange the existing patterns of medical and surgical care. In some instances, specialization leads to a significant change in the way specialties interact with each other.

This process is evolutionary and dynamic, and it attracts attention, because it modifies the status quo. Even so, the majority of those in such organizations as the American Board of Medical Specialties are on record as concluding that the growth of subspecialization is inevitable and is not inherently bad. What is particularly unpleasant, however, is the tendency for change to stimulate divisiveness and disparagement between competing groups—and this is what all of us should oppose. The most effective opposition can be found in efforts to work together toward common goals.

This editorial is stimulated by the publications of Drs Friedmann[1,2] and Jurkiewicz,[3] as they have caused a certain degree of introspection and analysis of the issue of fragmentation within our own specialty. In my opinion, their essays fail to mount a very convincing argument in terms of their implied thesis that general surgeons, on the basis of the breadth of their education, should be in charge of the field of head and neck surgery (and the other surgical specialties) as they were 50 years ago. On the other hand, they do alert us to some likely adverse outcomes within our specialty if we do not have the ability to accommodate change. As otolaryngology-head and neck surgery enters a new decade, we find ourselves at the same crossroads where general surgery stood in the 1950s. Most of our training programs are headed by general otolaryngologists-head and neck surgeons, and our curricula are designed to train very solid general otolaryngologists-head and neck surgeons. In part, this is a reflection of our history and the requirements for residency accreditation as developed by the Residency Review Committee for Otolaryngology. Certification by the American Board of Otolaryngology is based on an examination that emphasizes the broad categories of general otolaryngology, otology, facial plastic and reconstructive surgery, and head and neck surgery, but, in the eyes of the American Board of Medical Specialties, the certificate relates only to competence as a specialist in general otolaryngology.

Meanwhile, within our specialty, the process of subspecialization continues to advance. The first major areas of subspecialty interest were the fields of otology and bronchoesophagology. Head and neck surgery began to emerge in the 1950s followed by growth in our involvement in facial plastic surgery in the 1960s, and more widespread practice of otolaryngic allergy in the 1970s. Pediatric and geriatric otolaryngology and neuro-otology have taken some significant steps forward during the 1980s. There is no sign that the process of subspecialization is likely to slow during the 1990s. Each of these subspecialties is now seeking greater recognition and autonomy in one form or another.

But doesn't this sound like a parallel to the changes that took place in general surgery? Are we standing on the threshold of a period of fragmentation of general otolaryngology, and are we about to split into several adversarial camps because of our inability to hold together around a central core?

The answer to these questions will be "*yes*" if we continue to move along the paths that we have taken during the past few years. We have had a remarkable proliferation of subspecialty societies, subspecialty journals, subspecialty meetings, subspecialty fellowship programs, and now subspecialty board examinations. These developments serve to define an area of specialized interest, to foster its progress, and thereby to attract physicians to train and engage in the practice of that subspecialty. It is quite natural for these individuals to seek special forms of recognition for their expertise as subspecialists.

So far, the process seems progressive and positive. Individuals reach a level of competence in a general specialty, and then they build on that foundation by added training to become more qualified through additional education and experience. By virtue of their expertise (all other factors being equal), they should be able to attract enough physician and patient referrals to shape their practice along the lines of their special interests. This is quite an attractive prospect to many young medical students and physicians and it serves the public well. I am very impressed by the high percentage of residency applicants this year who intend at this stage of their careers to pursue subspecialty fellowship training after they complete their standard residency in otolaryngology-head and neck surgery. Well over half of the candidates we interviewed had such career plans.

So where is the downside in all of this dynamic change in the structure of our specialty? Where is the risk and the danger?

In my opinion, it is in much the same place as it was for general surgery several decades ago. The specialty may become enmeshed in a succession of fights over real and imagined conflicts among special interest groups. Some will be fights between general otolaryngologists and subspecialists, others will involve traditionalists (the establishment) vs new ideas and techniques (mavericks). Some conflicts will occur between older otolaryngologists and younger otolaryngologists. In short, we have the potential to experience the same "schisms between and among surgical disciplines" as described by Friedmann—only this time, *it will all be within our specialty.*

We do not have any particular quarrel at this point over subspecialty nomenclature or self-designation, nor do we have a major effort underway to expand one subspecialty at the expense of another. We do have some tension regarding specialized formal recognition of the additional training some individuals have received. Certificates and diplomas issued by the training institution or fellowship sponsor are not controversial and they should suffice as documentation that an individual has successfully pursued advanced training in a subspecialty. More formal processes such as added qualifications, subcertification, and the development of separate (non-American Board of Medical Specialists) board certification mechanisms are expensive, time-consuming, problematic, and extremely controversial. With each successive step, we reach new levels of subspecialty visibility and autonomy. Even the discussion of these latter processes tends to open up wounds between general otolaryngologists-head and neck surgeons and subspecialists.

So what can we project down the road if we pursue our present course of subspecialization and growing subspecialty autonomy? We can predict increasing erosion of the specialty core and a growing sense of anxiety on the part of general otolaryngologists-head and neck surgeons that their professional domain is shrinking and that many subspecialty surgical procedures are becoming riskier than they were before. It can be expensive for a generalist to have a complication that might have been avoided by a subspecialist. In terms of hospital credentials, professional liability issues, and patient referrals, the generalist is often at a disadvantage.

What can we learn from the experience we have observed in the case of general surgery? This is a profound question, and I doubt that any one individual can be certain of the answer, but I think we need to open some dialogue along the following lines:

1. How can we as a specialty avoid the error of a generalist group trying to maintain control of rapidly developing subspecialties and subspecialists?
2. How can we reduce the role of existing, rigid, monolithic, central hierarchies and increase the effectiveness of decentralized, task-oriented networks?
3. How can we develop more common bonds and unifying themes within our specialty and de-emphasize the less important issues that tend to be divisive?
4. How can we become more accepting of changes, internal and external, that alter the course of our specialty?
5. How can we keep our focus on the point that our specialty will have a significant voice within medicine *only* if we all hold the specialty together?
6. How can we keep our vision of molding this specialty into a healthy federation of subspecialties that invites the widest possible degree of participation in important planning and decision-making activities and consistently resolves difficult problems on the basis of solutions that serve our patients and the public best?

No, Dr Friedmann, we are not fretting or fighting over fragmentation, we are at odds concerning change. We ought to do our best to seek paths of cooperation and to work in a way that heals the rift that has developed between general surgery and otolaryngology-head and neck surgery. But a wound cannot heal if only one side is working to accomplish the healing process.

At the same time, we must look closely into our specialty for patterns that parallel those that we can find in the recent history of general surgery. Where we see those patterns emerging, we must be creative and committed to the quest for solutions that will diminish fragmentation.

Specialization is a powerful engine for change. Further specialization being inevitable, we would be wise to accept the certainty of more change and to lessen our grip on the past. Our real task is to manage the changes that are occurring in a manner that will lead to safer and more effective patient care.

In my view, the profession of Medicine is a community with more common goals than differences. The surgical disciplines are an important, but changing, neighborhood within the larger community. Our specialty is a relatively small family within this neighborhood and the family comprises several individuals with unique talents and aspirations. Our task is clear—we must find unity in the presence of diversity. I believe that we can and that we shall.

BYRON J. BAILEY, MD
Chief Editor

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Segmental Mandibular Regeneration by Distraction Osteogenesis

An Experimental Study

Peter D. Costantino, MD; George Shybut, MD; Craig D. Friedman, MD; Harold J. Pelzer, DDS, MD;
Michael Masini, MD; Maise L. Shindo, MD; George A. Sisson, Sr, MD

• We report the use of distraction osteogenesis for segmental mandibular regeneration. This technique has been used in thousands of patients in the Soviet Union to regenerate as much as 30 cm of tubular bone in the extremities. However, we are unaware of previous experimental or clinical reports of segmental mandibular regeneration by distraction osteogenesis. In a canine model, 2.5-cm segmental mandibular defects were filled with regenerate bone in 25 days at a rate of 1.0 mm/d using bifocal distraction osteogenesis. The diameters of the regenerate segments were comparable with preexisting mandible, and all animals resumed normal oromandibular function following regeneration. The regenerate bone was evaluated radiographically, angiographically, and histologically. In the control group without distraction osteogenesis, the segmental defects failed to fill with regenerate bone. The theoretical basis for distraction osteogenesis, a detailed description of the technique, and a review of previous studies on experimental mandibular lengthening are presented.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:535-545)

Functional and esthetic reconstruction of the mandible after bone loss continues to be a formidable problem in head and neck surgery. Grafts, flaps, and synthetic materials have been used to reconstruct the mandible. Unfortunately, grafts and flaps result in added morbidity, and may be of limited availability. Synthetic materials generally retain the characteristics of a foreign body and fail to fully replace the missing tissue in appearance or function. As a result, no uniformly successful method of reconstructing segmental mandibular defects exists.

An ideal situation for replacing lost mandibular bone would involve "growing" that replacement bone within the existing defect. The concept of regenerating bone in vivo is not new. For the last 80 years, surgeons, primarily in the field of orthopedics, have described procedures for lengthening bones in the extremities.[1-3] Several of these techniques have relied on the "stretching" of tubular bones to generate "new" bone and achieve lengthening. The process of generating new bone by stretching is called distraction osteogenesis (DO).

Recently, one method of DO has gained considerable popularity and notoriety as a way of reconstructing segmental bone defects in the extremities. This method was developed over the last 35 years by Gavriel A. Ilizarov of the Soviet Union. The technique has been used in thousands of patients for a variety of orthopedic problems within the Soviet Union,[4,5] and is now beginning to be used by Western surgeons. To quote Dr Ilizarov from a speech given as the 1987 Sir Robert Jones Lecturer of the Hospital for Joint Diseases Orthopaedic Institute (London, England): "This new method has given us the opportunity to . . . replace extensive bone and soft tissue [loss] . . . , to elongate limb segments by 30 cm and more; to thicken and reshape thin shanks; to correct and align severe bone and foot defor-

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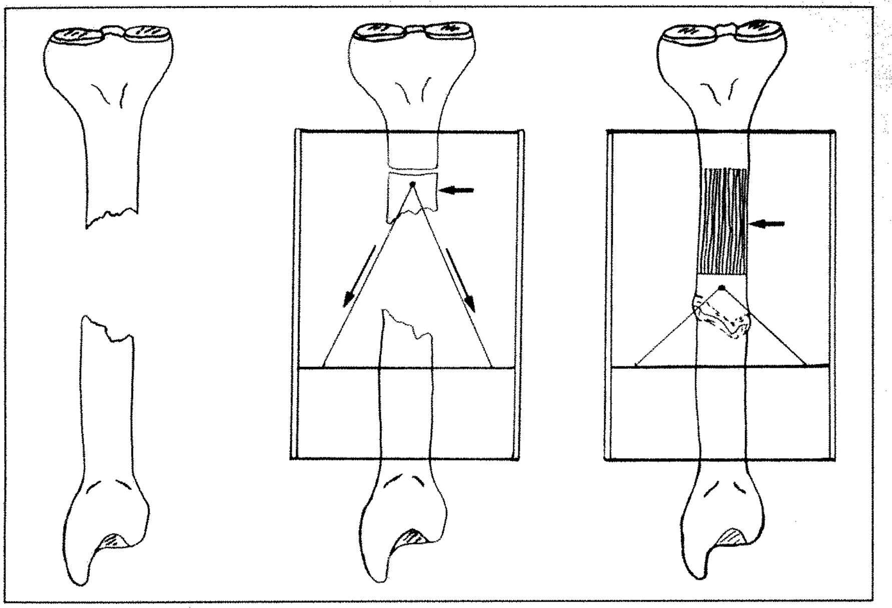

Fig 1.—General principles of bifocal distraction osteogenesis. Left, Segmental tubular bone defect. Center, The transport disk (arrow) has been cut from the proximal stump, and the distraction appliance placed. The arrows indicate the force vectors that will distract the transport disk away from the proximal stump. Right, The regenerate (arrow) is proximal to the transport disk, and the transport disk is in compression with the distal segment. The entire segmental defect has been closed without a loss of length.

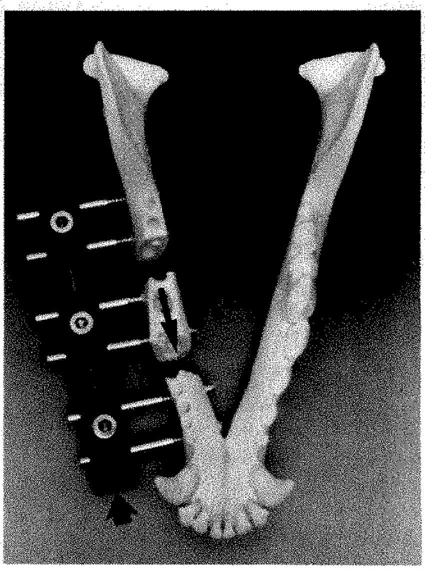

Fig 2.—The distraction appliance affixed to a preserved canine mandible. The transport disk can be seen midway between the proximal and distal mandible stumps. The direction of transport disk movement is indicated by the long arrow. The socket for turning the screw that moves the tram attached to the transport disk is in the distal end of the distraction appliance (short arrow).

mities; and to grow missing parts of limbs such as fingers and toes."[4]

One variant of Ilizarov's technique involves the distraction of a vascularized segment of bone, referred to as a "transport disk," which has been cut from the remaining stump in a long bone defect (Fig 1, left and center). When the vascularized bone disk is cut free, the periosteum and intermedullary soft tissue are preserved. The movement (distraction) of that vascularized transport disk of bone across the segmental defect leaves living bone in its wake in the form of a regenerative callous (Fig 1, right). This particular method of DO, employing a transport disk to achieve closure of a segmental defect, is referred to as "bifocal." The technique is bifocal because there is one area of regenerate bone formation and one area of compression osteosynthesis (where the transport disk unites with the opposite bony stump).

Various types of DO have been used experimentally to lengthen canine mandibles,[6-9] but have been limited by the quantity, location, and morphology of the bone generated. We were unable to find reports in the international literature of controlled animal or human experiments applying bifocal or any other type of DO to segmental mandibular reconstruction. Therefore, the purpose of this study was to evaluate the basic technical feasibility and morphogenic result when bifocal DO is applied to this problem. Dogs were chosen as the test subjects because they are a proven model for mandibular reconstruction.[6-9] Further, canine mandibles are long and narrow, thereby providing sufficient length for the placement of an external distraction appliance.

SUBJECTS AND METHODS

Six healthy adult 20- to 25-kg mongrel dogs served as the experimental subjects. The protocol and guidelines for this study were approved by the Institutional Animal Care and Use Review Committee of Northwestern University Medical School, Chicago, Ill. The animals were procured by the Northwestern University Medical School Center for Experimental Animal Surgery. The preoperative and postoperative care of these animals was overseen by the university veterinarians to insure proper and humane treatment.

Surgery was performed under sterile conditions using endotracheal halothane anesthesia after induction with intravenous 4% pentobarbital sodium (1 mL per 2.25 kg). After all operative procedures, the animals received buprenorphine hydrochloride (0.01 mg/kg intramuscularly) every 12 hours over 3 days for pain control. Keflin (40 mg/kg intramuscularly) every 12 hours for 3 doses was used for antibiotic coverage. The deposited osteoid was fluorescently labeled by feeding the animals 250 mg of tetracycline hydrochloride once each day.

Experimental Design

Group 1 (the experimental group) contained three animals. In this group, a segmental defect including periosteum was unilaterally created in the mandibular body, and a custom-made distraction appliance affixed to the mandible (Fig 2). The segmental mandibular defect and distraction appliance were placed and the transport disk was cut free during a single operation. This group was then reconstructed with bifocal DO. The distraction appliance was made by Orthofix SRL, Verona, Italy, and consisted of an external fixator with a screw-driven tram. A 360° revolution of the screw on the distraction appliance advanced the tram, and the attached transport disk of bone, by 1 mm. The general design of this distraction appliance was based on previous work by Wagner.[10]

Three animals in group 2 served as controls. As in Group 1, a segmental defect was created in the mandibular body. In contrast to group 1, group 2 animals had an external fixator (instead of a distraction appliance) applied to maintain the anatomic position of the proximal and distal mandibular stumps after creation of the segmental defect. Further, the periosteum bridging the segmental defect was preserved to permit maximum osteogenic potential in the absence of distraction. These animals were allowed to heal for 8 weeks to determine if the segmental mandibular defect, with surrounding periosteum intact, would be filled with regenerate bone without the use of distraction osteogenesis.

At the end of this 8-week period, the external fixator was removed from the group 2 animals and the stability evaluated. If the mandibular stumps were healed in anatomic position by a regrowth of bone across the segmental defect, regeneration in the absence of distraction was considered successful. If fibrous tissue or structurally inadequate bone bridged the segmental defect, then regeneration in the absence of distraction was considered a failure. If regeneration failed to occur, the external fixator was replaced by a distraction appliance, and the periosteum bridging the persisting segmental defect was removed to achieve the same situation as in the group 1 animals. Group 2 (control) animals then underwent the same process of distraction using the protocol applied to group 1 animals.

This experimental design tested two hypotheses: first, that bifocal DO can be used for the regeneration of segmental mandibular defects; and second, that DO is applicable to preexisting segmental mandibular defects.

Operative Technique

Two weeks prior to creation of the segmental mandibular defect, the teeth were removed over a 6-cm segment of mandible in each dog. Following the extractions, the gingiva was reapproximated with 4-0 chromic suture, and the animals were fed canned food for 14 days. We hoped that extracting the teeth beforehand would permit the gingiva to heal and allow the segmental mandibular defect to be created without intraoral contamination. Functionally, this was not achieved, as all of the animals had small defects in their gingiva after segmental osteotomy. Therefore, all distraction appliances were placed in a clean-contaminated surgical field.

An external incision was made parallel to the mandibular ramus on the edentulous side (Fig 3, top left), and the distraction appliance attached before creation of the segmental defect. This distraction appliance maintained the proximal and distal mandibular stumps in anatomic position and provided the mechanism by which the transport disk of bone could be moved across the segmental mandibular defect.

The distraction appliance was attached to the mandible by four horizontally directed, self-tapping stainless steel bicortical pins, which were 2 mm in diameter and 5 cm long. An aluminum template was used to guide the placement of the bicortical pins and to position the mandibular osteotomies (Fig 3, top center). This template assured a segmental defect of 2.5 cm and provided for perpendicular placement of the bicortical pins within the mandible. Two pins were placed 2 mm and 3 mm, respectively, from the end of each mandibular stump in the horizontal plane. These pins were then passed through the overlying skin through separate stab wounds.

A 2.5-cm segment of mandibular body was then removed without disturbing normal mandibular occlusion. In group 1, the 2.5-cm segment of mandibular bone and periosteum was removed by a through-and-through osteotomy on either side of the segment. Removing the surrounding periosteum along with the mandible served to parallel the situation encountered clinically during segmental mandibular resection for cancer.

Following creation of the segmental defect, the pins used to attach the transport disk of bone to the distraction appliance tram were placed. These pins were placed 1 to 2 mm from each cut surface of the transport disk, respectively, and passed through the overlying skin. After these two pins were firmly attached to the distraction appliance tram and the segmental defect was made, a transport disk of bone was cut from the proximal mandibular stump. The transport disk was 1.5 to 1.7 cm in width. Small differences in transport disk width resulted due to variations in osteotomy placement. Prior to cutting the transport disk free, the periosteum was circumferentially elevated from the mandible over the area of the planned osteotomy (Fig 3, top right). With the periosteum protected by retractors, an osteotomy was made with an oscillating saw. The entire intermedullary cavity, including the inferior alveolar artery, was transected in all animals (Fig 3, bottom left). Bleeding was controlled by tamponade alone. Care was taken to minimize trauma to the periosteum, and to preserve a vascularized soft-tissue cuff around the transport disk. With this osteotomy, the transport disk was freed entirely from the proximal mandible, with only a sleeve of periosteum attaching it to the surrounding soft tissue. The distraction appliance was then reversed to approximate the transport disk with the stump of the proximal mandibular segment.

The procedure was concluded by irrigation of the wound with sterile saline. Gingival defects were closed with 4-0 chromic suture, and the external incision closed in layers using 3-0 polyglactin 910 sutures. The wounds were not drained in any of the animals.

Group 2 (controls) differed from group 1 in that the periosteum was preserved over the region of the segmental mandibular defect, and an external fixator, rather than a distraction appliance, was placed before segmental mandibular resection. Eight weeks later, if regeneration did not occur, the periosteum across the persistent defect was removed, and the external fixator replaced by a distraction appliance. A transport disk was freed from the proximal stump by the same technique, and distraction begun under the same protocol as with group 1 animals. This served to achieve the same, but delayed, operative situation as the animals in group 1.

Postoperative Protocol

The animals were allowed to heal for 10 days following placement of the distraction appliance to allow repair of defects in the periosteum and endosteum, and to permit an osteoid callous to form at the interface of the transport disk and the proximal mandibular stump (Fig 3, bottom center). Beginning on day 11 the transport disk was advanced 0.25 mm four times per day for a total of 1 mm each day. It took approximately 25 days for the transport disk to traverse the 2.5-cm defect.

On completion of advancement, under thiamylal sodium sedation, the anterior surface of the transport disk and posterior surface of the distal mandibular stump were cleaned of overlying soft tissue by passing an oscillating saw between them through a small incision in the gingiva. This was done to prevent nonunion of the transport disk to the distal mandibular stump (Fig 1, right). Nonunion was probable due to the amount of soft tissue that consistently became entrapped between the transport disk and distal mandibular stump during advancement of the transport disk.

At this point, a solid mass of immature bone extended from the posterior surface of the transport disk to the proximal mandibular stump (Fig 3, bottom right). The distraction appliances were left in position for 4 weeks to allow this immature bone to calcify and achieve sufficient structural strength for function without the presence of the distraction appliance. Karp et al[9] reported that 4 weeks was an adequate period for structural calcification of regenerate bone. This period of external fixation also permitted the transport disk to unite with the distal mandibular stump by compression osteosynthesis, thereby reconstituting the continuity of the mandible. The distraction appliance was removed under 4% so-

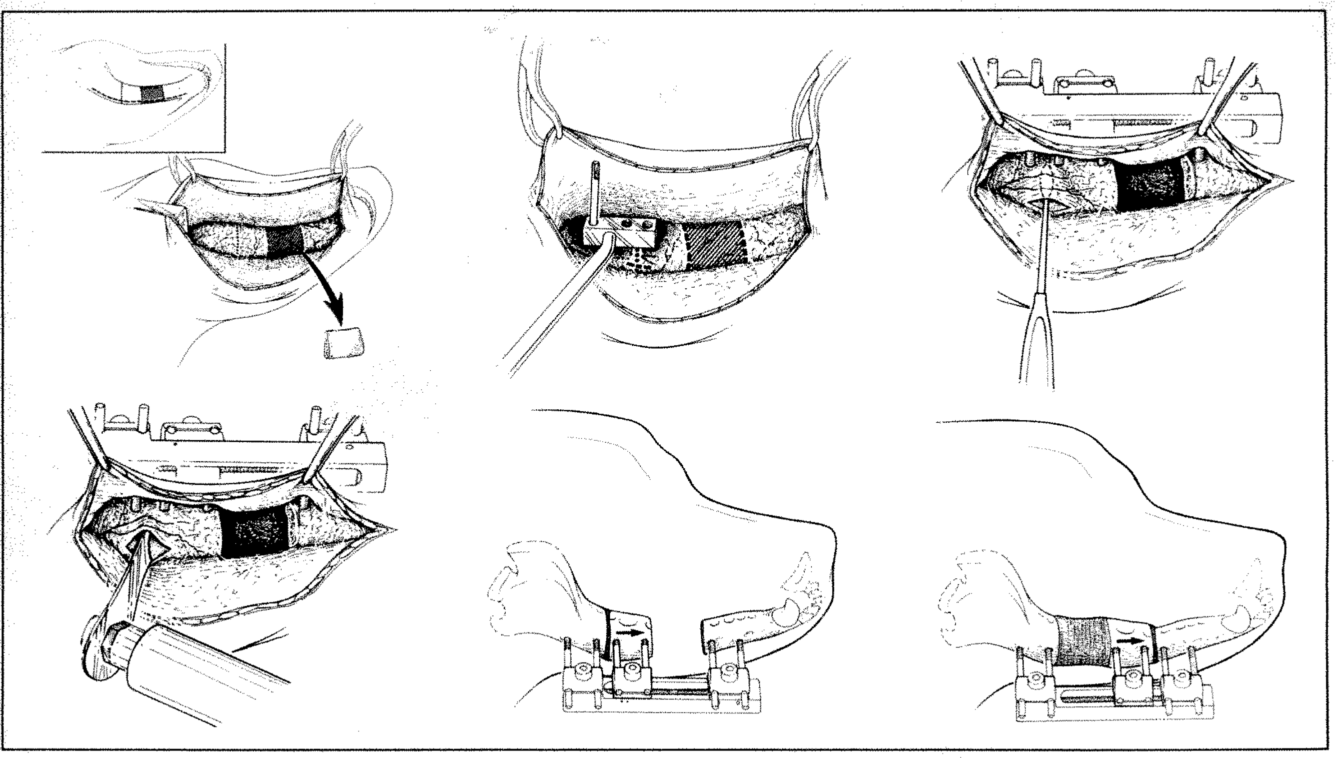

Fig 3.—Operative technique. Top left, Exposure of the mandibular body with preservation of the surrounding soft tissue and periosteum. Shaded region shows where the segmental defect will be created. Top center, Placement of the drill template and bicortical pins. Top right, Circumferential elevation of the periosteum off the mandible where the transport disk osteotomy will be made. With the distraction appliance in place, the segmental defect was created. Bottom left, Placement of the periosteum-sparing osteotomy with an oscillating saw. Bottom center, Early regenerate formation between the transport disk and the proximal stump. Arrow indicates direction of movement of the transport disk during distraction. Bottom right, At the completion of distraction, the transport disk is in contact with the distal mandibular stump, and the segmental defect is filled with regenerate.

dium pentobarbital sedation (1 mL per 3.15 kg).

The criteria for successful reconstruction were (1) complete reconstitution of the missing mandibular segment, (2) functional fusion of the transport disk to the distal mandibular stump, and (3) a structurally and functionally stable mandible without the use of an external fixator. Functional fusion and stability was determined by permitting the animal to eat hard-pellet dog food for 2 weeks after reconstruction and removal of the external fixator. After the 2-week observation period, the animals were killed with intravenous Buthanasia-D (0.4 g per milliliter of pentobarbital; 1 mL per 4.5 kg).

Data Management and Analysis

Radiography.—Oblique roentgenograms of each mandible were taken with a roentgenogram machine (Litton Industries, Beverly Hills, Calif) at 50 kV and 4 mA following placement of the distraction appliance. Roentgenograms were also taken at the completion of disk transport and at 2-week intervals until death. Additional roentgenograms were taken of group 2 (control) dogs after creation of the segmental mandibular defect, and just prior to conversion from an external fixator to a distraction appliance.

Angiography.—Angiograms of the experimental and control mandibles were obtained in each animal. The method of angiography did not permit survival following the angiogram; therefore, the studies were done immediately prior to death. Under general anesthesia, a 16-gauge, 2-in catheter (Angiocath, Deseret Medical Inc, Parke-Davis & Co, Sandy, Utah) was inserted into the common carotid artery under direct vision through an external incision. Thirty milliliters of Hypaque-M 75 or 90 was infused by hand with a 60-mL Luer-Lok syringe approximately 3 seconds before activation of the roentgenogram unit (50 kV and 4 mA). Only a single angiogram of each animal was obtained.

Histologic Examination.—After death, the entire mandible and surrounding periosteum were removed intact from each animal. The mandibles were then sectioned through the symphysis. In four of the animals, two from each group, the resultant hemimandibles were sectioned through the long axis over the entire length using a band saw. Coronal sections of the hemimandibles in the remaining group 1 and group 2 animals were obtained. The sections were decalcified in 12% hydrochloric acid solution and embedded in paraffin; representative sections were stained with hematoxylin-eosin, trichrome stain, and toluidine blue.[11]

The hematoxylin-eosin- and trichrome-stained sections were examined using a light microscope (Olympus BH-2) at magnifications of ×4 and ×10. The tetracycline-labeled sections were examined under fluorescent light through a microscope of the same model at the same magnifications. Histologic sections were evaluated by a board-certified pathologist with expertise in ossified tissues.

RESULTS

Functional and Morphologic Results

All subjects survived the duration of the experiment, and the distraction device was removed from all of the animals without difficulty 4 weeks after complete regeneration. There was adequate structural integrity of the reconstituted mandible, with firm union of the transport disk to the distal mandibular stump. All of the animals were able to begin eating canned food on the first postoperative day, and hard-pellet food 4 weeks after the segmental mandibular defect had been closed. In summary, all of the animals met all of the necessary criteria for successful reconstruction.

In group 2 (controls), the segmental defects were not filled with functionally significant regenerate bone without the use of DO. A small amount of bone was deposited within the periosteal sleeve surrounding the segmental defect, but this bone was not structurally stable after removal of the external fixators. There were no technical problems in converting the control animals to a distraction appliance, and there were no functional differences between group 1 and group 2 (control) animals during the process of distraction. Further, there was no difference between the two groups in the quality or quantity of the regenerate bone, or in the function of the animals following reconstruction.

The regenerate segment was comparable in diameter with the transport disk in all specimens. During distraction, the regenerate segment could not be readily distinguished from preexisting bone by palpation. After death, the exact location of the junction between the regenerate and the preexisting bone could not easily be determined (Fig 4, top). On sagittal section, in all of the group 1 animals and two of the group 2 dogs (five total), the inferior alveolar canal and artery were found to be recanalized. The inferior alveolar nerve did not regenerate in any of the animals, but was found to terminate just proximal to the transport disk osteotomy site. Grossly, an outer cortical layer and trabecular medullary cavity could be seen in all specimens (Fig 4, bottom).

Observations and Complications

The animals had no difficulty receiving adequate oral nutrition during the study and demonstrated no physical deficit from the presence of the distraction appliance. Advancing the transport disk did not cause any apparent discomfort.

The gingiva anterior to the transport disk tended to be pushed ahead of the disk as transport progressed. We had assumed that the transport disk would "slide" beneath the gingiva, but this was not the case. Instead, soft tissue was generated around the regenerate segment and transport disk. The gingiva surrounding the transport disk and regenerate segment remained intact, and the mandibular bone was not exposed during the distraction process. The generated gingiva over the region of the transport disk and regenerate segment was significantly more adherent to the bone than "normal" gingiva.

Although there were no serious perioperative complications, two of the animals did develop minor infections at two pin insertion sites. These infections were successfully treated with a 5-day course of cephalothin sodium (40 mg/kg intramuscularly every 12 hours) along with cleaning the pin insertion sites with hydrogen peroxide twice a day. The infections developed 2 weeks and 3 weeks after placement of the distraction appliance, respectively. Cultures of the drainage revealed pri-

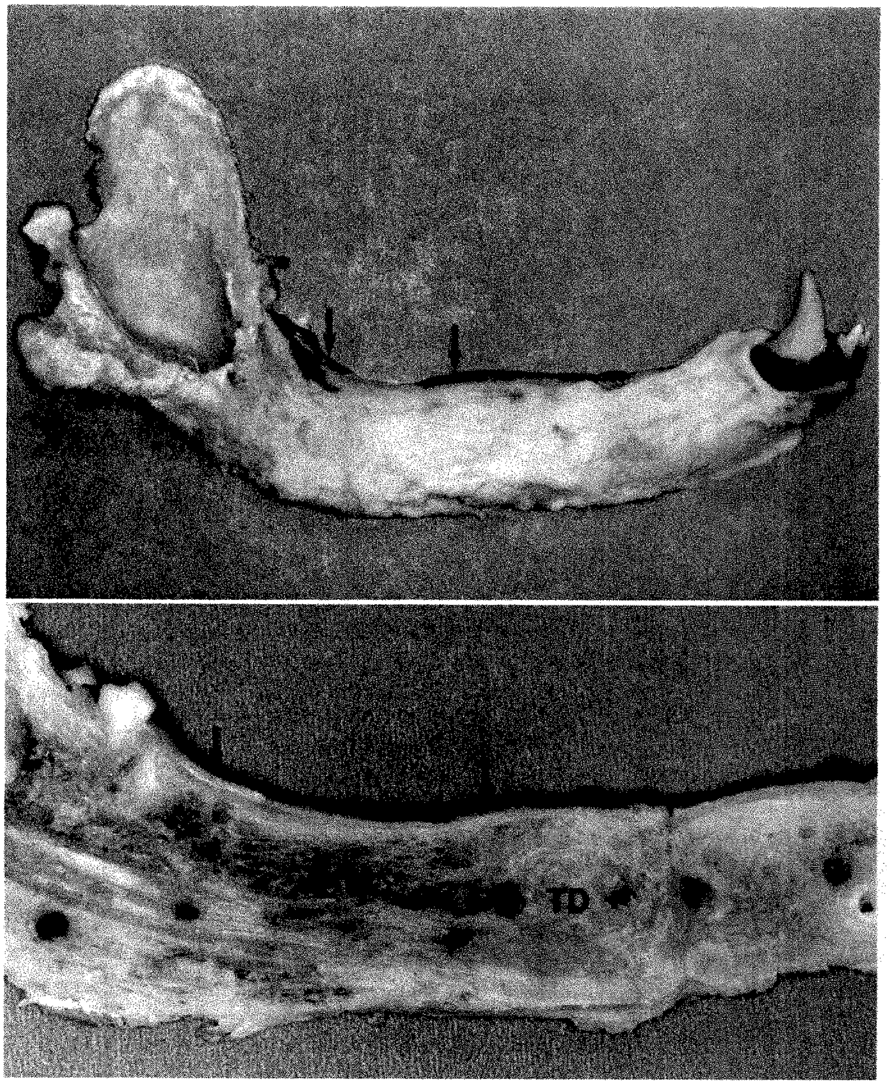

Fig 4.—Gross appearance. Top, Outer surface of the reconstructed mandible. The diameter of the regenerate (between arrows) is the same as that of the preexisting mandible. Bottom, Note the outer cortical layer and inner trabecular bone in the regenerate segment of this sagittal section. The regenerate segment is between the arrows, and the transport disk is labeled TD. The inferior alveolar canal and artery have recanalized through the regenerate segment and transport disk.

marily *Staphylococcus* species sensitive to cephalothin.

One animal developed a salivary retention cyst posterior and inferior to the ipsilateral mandibular angle, presumably due to intraoperative injury to the submandibular gland. The aspirated contents of the cyst contained no bacterial growth. This animal was in the control group (group 1), and the cyst developed after the initial surgery when the segmental defect was created and the external fixator applied. The cyst was excised without any subsequent problems when the animal was converted from an external fixator to a distraction appliance during the second operation.

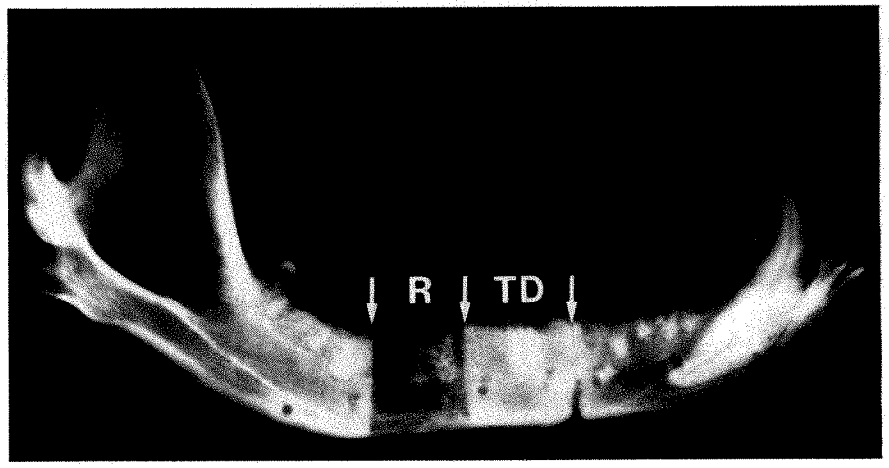

Fig 5.—Roentgenogram of a reconstructed hemimandible. Note the radiolucent appearance of the regenerate segment (R) compared with the transport disk (TD). There are vertical bands of varying calcification within the regenerate. This is a different specimen than that seen in Fig 4.

Radiographic Examination

The control animals (group 2) all demonstrated small amounts of radiopaque osteoid tapering from each mandibular stump toward the center of the segmental defect at the end of the 8-week healing period. This bone was "patchy" in appearance and discontinuous in structure. These small amounts of regenerate bone did not radiographically bridge the segmental defects in any of the group 2 animals, and did not represent structurally stable bone after removal of the external fixators.

After the first 2 weeks of distraction, the regenerate bone was radiographically shown to have the same density as the surrounding soft tissue, even though the reconstructed area felt no different from the preexisting mandible on palpation. At 3 to 4 weeks after initiating distraction, radiopaque material tapered from the surface of the transport disk and proximal stump to the center of the regenerate. A central, vertically oriented, radiolucent zone existed at that time. By 7 to 8 weeks, when the external fixator was removed, the entire regenerate showed progressive calcification. At death, 10 to 11 weeks after distraction began, dense but nonhomogeneous bands of calcification could be seen throughout the regenerate (Fig 5). At this stage, the regenerate was still less radiographically dense than preexisting mandible.

In two of the group 1 specimens, several small linear fractures could be detected in the regenerate. Several of these fractures were horizontal, others were vertically oriented, but none were transcortical. No fractures or areas of nonunion were identified in the other specimens. No functionally significant fractures occurred in any of the subjects.

Angiographic Examination

In five of the six animals, the inferior alveolar artery filled with contrast up to the distal (anterior) mandibular stump (Fig 6, top). The inferior alveolar artery recanalized through the regenerate segment and transport disk, but did not go on to anastomose with the primary nutrient artery of the distal mandibular stump. This was confirmed on gross examination of horizontally sectioned mandibles (Fig 4). Radiographically, a plexus of smaller vessels could be seen around the regenerate segment and the transport disk, which were not present on the unoperated side (Fig 6, bottom). In one of the group 2 animals, the inferior alveolar artery did not regenerate, but instead developed a significant arterial plexus surrounding the entire regenerate and transport disk.

Histologic Examination

The trichrome-stained sections of the regenerate demonstrated partially calcified woven bone in all specimens. With this stain, the connective tissue and nuclear material stained blue, while calcified bone and cytoplasm stained red. The blue-staining regenerate can be seen in Fig 7, top left and top right. This regenerate was separated by numerous vascular channels aligned in the direction of distraction. When cut horizontally (sagittally), these channels formed eclipses (Fig 7, top left and top right), but on coronal section took on a more circular configuration (Fig 7, bottom). Areas of neocalcification (red), primarily abutting the vascular channels, could be seen in the regenerate bone (Fig 7, top right).

Various stages of bone maturation could be seen within the same specimen, with the more recently deposited regenerate showing less calcification. Regenerate bone closer to the proximal stump and transport disk demonstrated more advanced calcification, while the central area of the regenerate segment contained the most immature bone. The mature bone of the proximal mandibular stump is the red material on the left half of Fig 7, top left. This mature bone is more dense but less cellular and vascular than the regenerate. No areas of fracture, fibrous union, or rupture were found in any of the specimens. There were no histologic differences between the regenerates in group 1 and group 2.

Evaluation of the tetracycline-labeled sections confirmed osteoid (immature bone) deposition in the region of the regenerate in all specimens, and demonstrated a reparative callous at

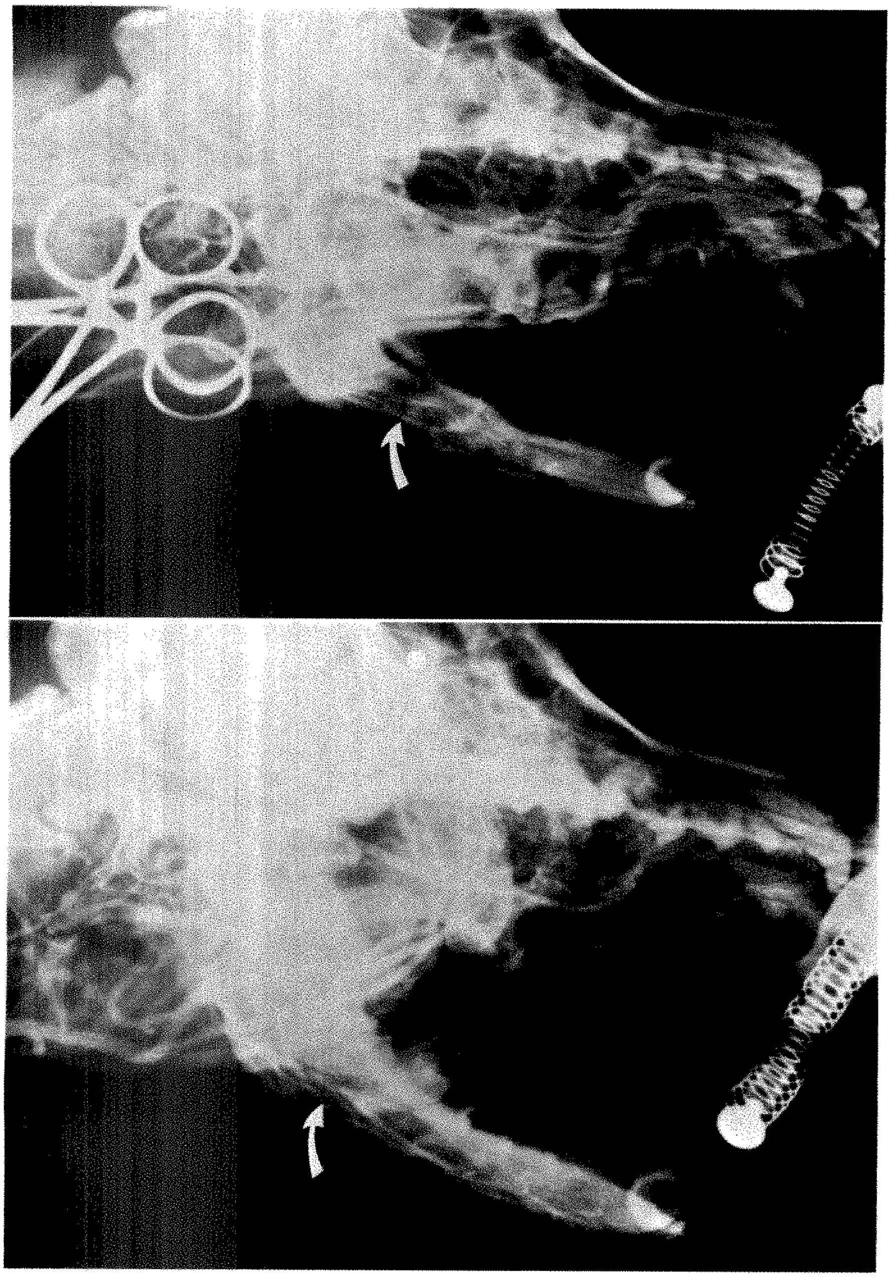

Fig 6.—Angiography. Top, Angiogram of the reconstructed side. The arrow demonstrates the regenerated inferior alveolar artery, which has recanalized through the regenerate segment and transport disk. Bottom, Angiogram of the unoperated side. The arrow demonstrates the intact inferior alveolar artery.

the junction of the transport disk and the distal mandibular stump. There was no evidence of osteoid deposition within the transport disk or in other preexisting areas of the mandible in any of the specimens.

When tissue from the persisting segmental defects of the initial stage of group 2 (controls) was sectioned, small amounts of osteoid were seen. The new bone was discontinuous and had a maximum diameter of 3 mm (Fig 8). Fibrous tissue and periosteum surrounded the islands of osteoid.

COMMENT

Distraction osteogenesis only defines the neoformation of bone by "stretching," and Ilizarov's technique is only one method of DO. Within the Soviet Union, Ilizarov's method of DO has been used to reconstruct bones in the extremities for over 35 years, and has proven to be the most flexible and reliable method of regenerating tubular bone.[4,5,12,13] More recently, the application of DO has expanded beyond the tubular bones of the extremities to include treatment of traumatic and congenital deformities of the small bones in the hands and feet. Considering the success of this technique within orthopedics, it is surprising that DO has not been applied to craniofacial and oromandibular deformities.

The site at which the bone is cut, and where regenerate bone will be deposited with DO, can vary.[13] If a long bone is too short, a single bone could be used to separate that long bone into two segments. Distraction of these segments would cause regenerate to be deposited between them as they move apart. This type of DO is monofocal, denoting one region of regeneration (Fig 9, left). If a transport disk of bone is used to reconstruct a segmental defect, as in this study, then it is considered bifocal (Fig 9, center). It is bifocal because there is one region of regenerate formation (behind the transport disk) and one area of compression osteosynthesis (where the transport disk eventually unites with the distal segment). If a transport disk is cut from each stump in a tubular bone defect, and the transport disks are advanced simultaneously, then two areas of regenerate bone and one area of compression osteosynthesis would result. Therefore, this variety of DO is trifocal.

There have been previous canine studies using monofocal DO for mandibular lengthening; none of these studies employed DO for segmental mandibular regeneration. One of the first such experiments was described in 1973 by Snyder et al.[6] In that study, canine mandibles were unilaterally shortened by 1.5 cm and allowed to heal, resulting in a significant crossbite. A through-and-through osteotomy was then made on the shortened side, and after a 7-day delay, distraction of the reparative callous was begun at 1 mm/d. Distraction was applied by a screw-driven external fixator attached to the mandible with

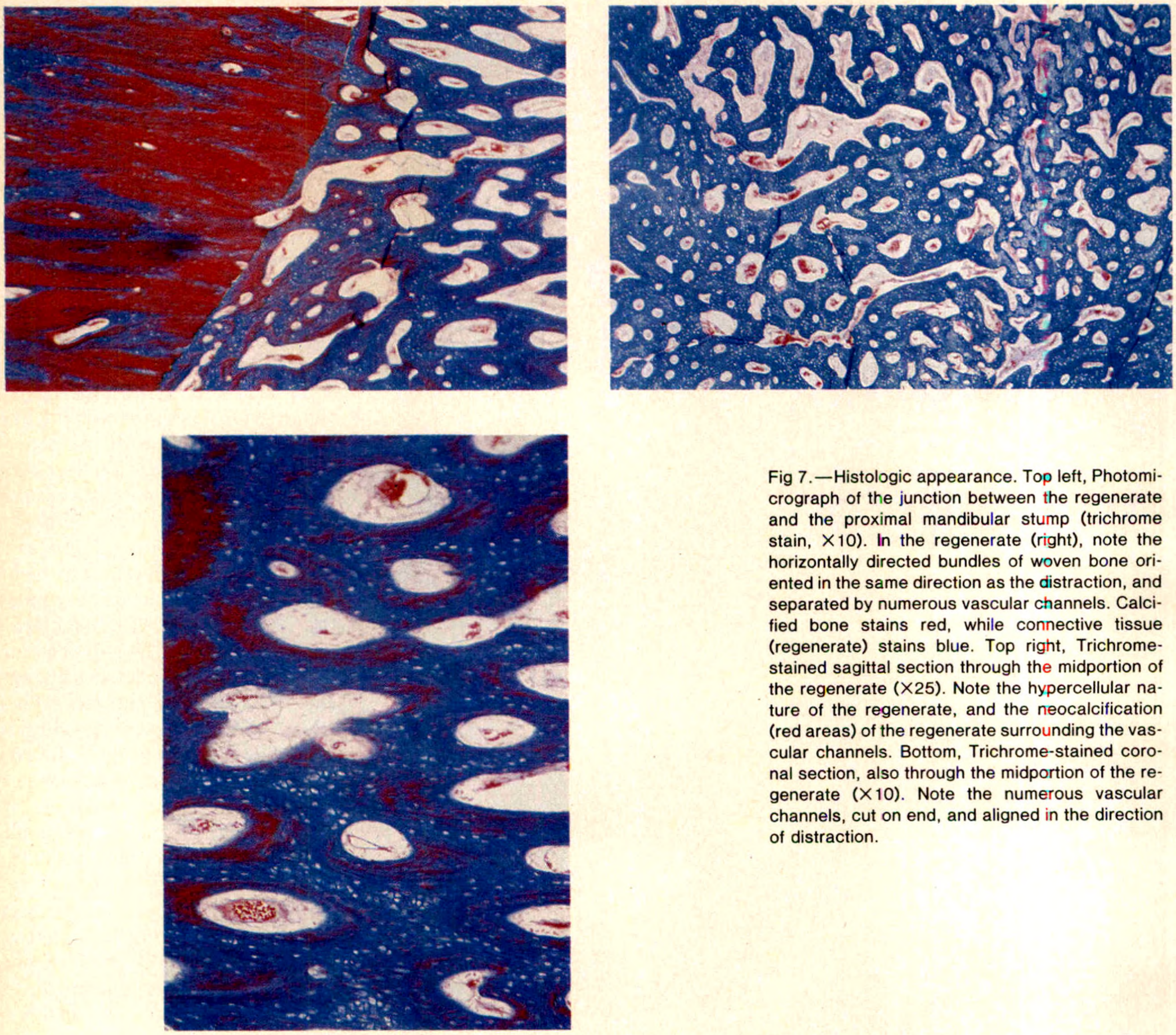

Fig 7.—Histologic appearance. Top left, Photomicrograph of the junction between the regenerate and the proximal mandibular stump (trichrome stain, ×10). In the regenerate (right), note the horizontally directed bundles of woven bone oriented in the same direction as the distraction, and separated by numerous vascular channels. Calcified bone stains red, while connective tissue (regenerate) stains blue. Top right, Trichrome-stained sagittal section through the midportion of the regenerate (×25). Note the hypercellular nature of the regenerate, and the neocalcification (red areas) of the regenerate surrounding the vascular channels. Bottom, Trichrome-stained coronal section, also through the midportion of the regenerate (×10). Note the numerous vascular channels, cut on end, and aligned in the direction of distraction.

bicortical pins. The length of the regenerate segment was 1.5 cm, and the crossbite was corrected in all animals. Snyder et al used the same advancement protocol as Ilizarov, which is interesting in that their work was done before there was a general knowledge of Ilizarov's methods within the United States. The article by Snyder et al was a preliminary report that did not indicate the number of animals in the study or histologically examine the regenerate bone. Further, they did not comment on whether the periosteum or intermedullary soft tissues were preserved.

Michieli and Miotti[7] in 1976 were able to lengthen the mandibular body in two dogs by 0.5 and 1.5 cm using an intraoral distraction appliance attached to the mandibular dentition. The periosteum and intermedullary soft tissues across the osteotomy were not preserved. Similarly, Kutsevliak and Sukachev[8] in 1984 used an intraoral dental distraction device to lengthen the mandibular body in 24 dogs by a maximum of 1.2 cm. They performed a circular corticotomy, as described by Ilizarov, to preserve the intermedullary contents. It is unclear whether the surrounding periosteum was also preserved. The rate of distraction employed by Kutsevliak and Sukachev was significantly slower than that suggested by Ilizarov, resulting in premature ossification of the regenerate and less lengthening. To our knowledge, this represents the first report available to Western scientific literature of Ilizarov DO (of the monofocal type) applied to the mandible.

Most recently, Karp et al[9] unilaterally lengthened the mandibles of six dogs by 2 cm each using a screw-driven external fixator similar to the one employed by Snyder et al.[6] They did not remove a segment of mandible, but unilaterally lengthened the mandible by monofocal DO. Although they created a crossbite, their study was sim-

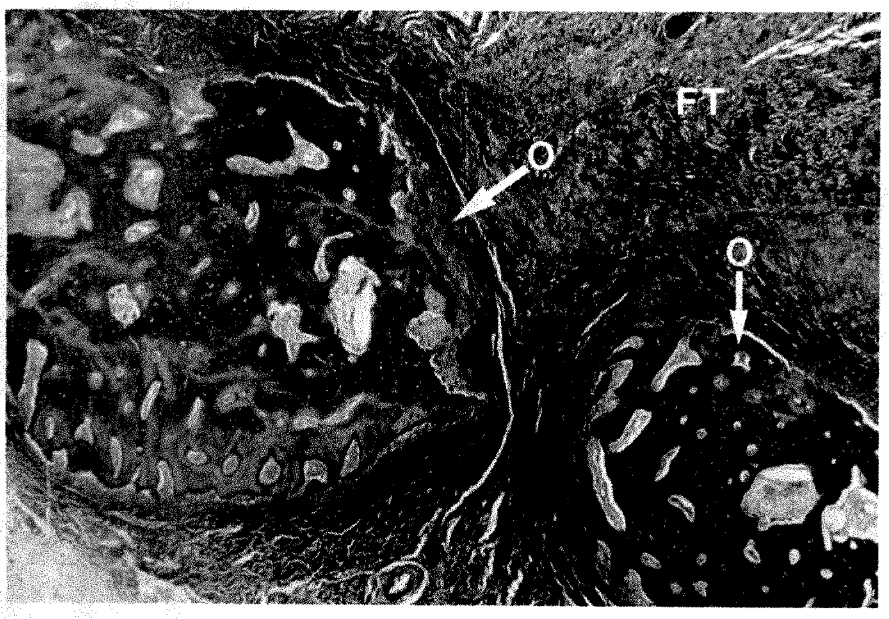

Fig 8.—Trichrome-stained section of tissue taken from the segmental defect in a control animal. Note the two foci of bone formation (labeled O) surrounded by fibrous tissue (labeled FT). The foci of bone in this photomicrograph measure less than 1.5 mm in diameter.

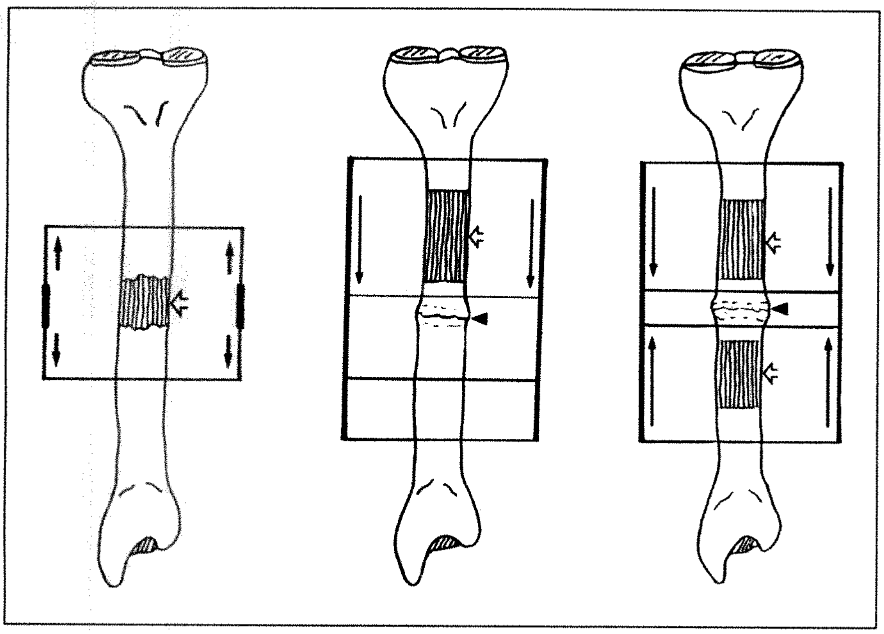

Fig 9.—Variations in Ilizarov distraction osteogenesis (DO). Left, Monofocal DO (open arrow indicates single area of regenerate). Center, Bifocal DO (open arrow indicates area of regenerate; arrowhead, area of compression osteosynthesis). Right, Trifocal DO (open arrows indicate areas of regenerate; arrowhead, area of compression osteosynthesis).

ilar to that of Snyder et al. Karp et al also evaluated the regenerate histologically and employed monofocal DO instead of a standard osteotomy. To our knowledge, there have been no reports of segmental mandibular reconstruction by DO.

In the setting of a significant segmental mandibular defect, bifocal DO has several distinct advantages over monofocal DO. First, in bifocal DO, the mandibular stumps at each end of the segmental defect do not need to be brought into contact, as is necessary with monofocal DO. Achieving contact between the stumps would only be possible for small defects primarily located in the body or angle of the mandible, or in an attempt to correct a preexisting hypoplastic or asymmetric mandible. Monofocal DO would not be applicable to significant segmental defects or any defect that extends around the arch of the mandible. Further, monofocal DO can only deposit bone in a straight line, ie, the line generated by separating the mandibular stumps. In contrast, bifocal DO should be capable of generating bone over an arc by employing a curved distraction appliance. Controlled animal studies are necessary to verify that distraction over an arc is feasible.

Because a transport disk can be cut from each mandibular stump, regeneration could progress from both ends of a defect. As previously described, this would represent trifocal DO (Fig 9, right).[12] Because the maximum rate of distraction is relatively fixed at 1.0 to 1.5 mm/d, distracting from each end of the segmental defect would decrease the time necessary to fill the defect in half, ie, a maximum rate of 2.0 to 3.0 mm/d. Trifocal DO has been successfully performed in the extremities of humans.

It was originally believed that the intermedullary arteries must be preserved for the successful formation of regenerate bone. More recently it has been confirmed that adequate osteogenic potential for bone regeneration exists within the periosteum alone.[13] After fracture, a significant component of the reparative callous that develops is produced by the periosteum.[14,15] Although preservation of the intermedullary blood supply has been shown to optimize regenerate formation, preservation of that blood supply is not absolutely necessary for success. Delafortrie (as cited by Paley[13]) determined in a canine tubular bone model that regenerate formation was not hampered if vascularized periosteum was preserved. He further determined that the primary nutrient artery recannulized within the first week after complete transection of the intermedullary vessels and soft tissue. Our results support these findings. In our study, the osteotomy used to free the transport disk transected all of the vessels and soft tissue within the intermedullary space of the mandible, but preserved the surrounding periosteum. After regeneration of the segmental defect, angiography demonstrated an extensive vascular plexus around the regenerate and transport disk, with regrowth of the intermedullary artery through these segments (Fig 6, top).

Employing a through-and-through osteotomy to free the transport disk, as we did, is a significant deviation from the "classic" Ilizarov technique. Ilizarov performs a corticotomy, rather than an osteotomy, to free the transport disk. Further, the corticotomy is made with an osteotome rather than a saw, and the transport disk is finally freed by gently fracturing the intermedullary bone at the site of the corticotomy. In this way, not only the periosteum but also the intermedullary soft tissues are preserved. A complete osteotomy using an oscillating saw was performed in this study based on the previously mentioned findings of Delafortrie,[13] and on the fact that the primary blood supply to the membranous bone of the mandible is via the periosteum. Further, the use of an oscillating saw rather than an osteotome simplified and facilitated creation of the transport disk. Freeing the transport disk with a complete osteotomy rather than an Ilizarov-style corticotomy does not appear to interfere with regenerate bone formation in the mandible.

Although the method of osteotomy in this study was "open," via an external incision, the soft tissue attached to the periosteal cuff surrounding the transport disk was meticulously preserved. Further, advancement was delayed by 10 days to permit repair of periosteal and endosteal damage and to allow for initial callous formation. This delayed "stretching" of the reparative callous has been termed "callotasis."[16,17] Panikarovski et al[18] reported that the optimal delay in initiating distraction in a canine mandibular model was from 14 to 21 days following corticotomy. They used monofocal DO to unilaterally lengthen canine mandibles. They found that beginning distraction before days 7 to 10 or after day 25 resulted in fibrocellular tissue deposition instead of osseous regeneration. In our study, distraction was begun after a delay of 10 days, yet only osseous regenerate, without fibrocellular tissue, was deposited.

Group 2 results confirmed the existence of significant osteogenic potential in the periosteum. Osteoid was deposited within the periosteal sleeve of the segmental defect in the group 2 animals. This was confirmed radiographically and histologically (Fig 8). The quantity of the bone deposited, however, was minimal compared with the amount generated through the use of DO. Further, the controls confirmed that preserving the periosteum with adequate external stabilization would not result in a functional regrowth of the canine mandible. Distraction osteogenesis was necessary for adequate, functional regenerate bone formation.

The control group (group 2) also demonstrated that the distraction appliance does not need to be applied primarily. In this group, the distraction appliance, and periosteum-sparing osteotomy, were placed 8 weeks after creation of the segmental defect without a demonstrable decrease in regeneration potential. Preexisting experimental mandibular defects are suitable for reconstruction by DO.

The radiographic results of this study paralleled previous experimental and clinical findings in the extremities.[12,13] There was progressive calcification of the regenerate over time, with a central radiolucent area persisting within the regenerate during the entire distraction process. This central radiolucent zone corresponds to a "pseudo-growth plate," which is the location of active bone deposition during distraction in the extremities. Similar to the findings in the extremities, calcification of the regenerate bone progressed over time from the periphery toward the center of the regenerate segment. Although none of the specimens in this study were radiographically shown to become as dense as the preexisting mandible, we expect that over time the regenerate would calcify to the same degree as normal mandibular bone.[12]

Plain roentgenograms demonstrated small linear fractures that were not bicortical in two of the specimens. The presence of these fractures suggests that the regenerate bone was not structurally strong enough to withstand the stress of mastication either when the external fixator was removed or when the dog began eating hard food. If the external fixator had been allowed to remain in place, or if soft food was eaten for a longer period, further calcification of the regenerate bone might have prevented these fractures. The fractures occurred in two of the six dogs and did not interfere with the functional success of the reconstruction in either animal.

Histologic examination of the regenerate showed a similar architecture to that seen in the tubular (long) bones, demonstrating bone in various stages of maturation.[19] In biopsy specimens of human regenerate, Tajana et al[20] confirmed the presence of multiple stages of maturation within the same specimen. These various stages of maturation are thought to lead to the eventual remodeling of the regenerate to form mature lamellar bone. Over time, the regenerate eventually takes on the same morphologic, histologic, and radiographic appearance of the bone that it replaced.[19]

In this study, all animals developed stable regenerate bone, resulting in complete rehabilitation of oromandibular function. There was no difference in the capacity for regeneration between primarily reconstructed animals (group 1) and the delayed group (group 2). Further, the animals functioned well during and after reconstruction.

The primary clinical use of this technique will be in oromandibular rehabilitation of patients with head and neck cancer. If used in a patient with cancer, several questions must be considered. First, how long will it take to regenerate a given segment of mandible, and can radiation therapy be given before regeneration is completed? Second, what effect will radiation have on previously formed regenerate bone, or on the regenerative capacity of a mandible after irradiation? Third, what effect will chemotherapy have on the regenerate bone, or on the regenerative capacity of the preexisting mandible? Preliminary studies suggest that regeneration, though decreased, will continue while chemotherapeutic agents are being administered.[21] However, these studies were done in rabbits, a species in which osseous growth is significantly different from humans.

Several basic technical problems will need to be addressed before DO is generally applicable in humans. First, movement of the transport disk results in a scar because the bicortical pins, which attach the transport disk to the distraction appliance, cut through the skin of the face. Further, regeneration around the mandibular arch could result in trauma to the marginal mandibular nerve as the pins pass through the soft tissue of the face below the oral commissure. In addition, the technical factors relating to the use of pedicled or free flaps with DO will need to be addressed. Considering the current methods of oromandibular rehabilitation, DO does have significant clinical potential in humans. Only strictly controlled animal and clinical trials of DO will determine what situations are appropriate for this method of mandibular reconstruction.

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Original Articles

Histotoxicity of Cyanoacrylate Tissue Adhesives

A Comparative Study

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• Cyanoacrylate derivatives have been used as surgical adhesives for many years. Shorter-chain derivatives (methyl- and ethyl-cyanoacrylate) have proved to be histotoxic. Longer-chain derivatives (butyl- and isobutyl-cyanoacrylate) are much less histotoxic. Many surgeons continue to use ethyl-2-cyanoacrylate (Krazy Glue) despite the availability of a less toxic derivative, butyl-2-cyanoacrylate (Histoacryl). In this study, the histotoxicity and bone graft–cartilage binding ability of Krazy Glue and Histoacryl were compared. Bone grafts harvested from the anterior wall of the maxillary sinus were placed in a subcutaneous pocket and glued to auricular cartilage in the rabbit. Krazy Glue and Histoacryl were used in opposite ears, harvesting specimens at 1, 2, 4, 12, 24, and 48 weeks. The Krazy Glue–treated ears developed seromas with histologic evidence of acute inflammation, tissue necrosis, and chronic foreign body giant cell reaction. The Histoacryl-treated ears showed mild acute inflammation and mild foreign body giant cell reaction. The Krazy Glue was completely degraded within 12 months, while some Histoacryl was still present at 1 year. Histoacryl had minimal histotoxic effect and good bone graft–cartilage binding ability, whereas Krazy Glue demonstrated severe histotoxicity.

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In quest of the ideal tissue-bonding agents, cyanoacrylate derivatives have been alluring in their ease of application, polymerization in the presence of moisture, adequate polymerization time, and strong yet flexible bond. Cyanoacrylates were first synthesized by Ardis in 1949.[1] One method of synthesizing cyanoacrylates is by reacting formaldehyde with alkyl cyanoacetate to obtain a prepolymer, then depolymerizing the material by heating to distill off the liquid monomer (Fig 1). It is possible to prepare several different cyanoacrylate compounds by altering the alkoxycarbonyl group (−COOR) of the molecule (Fig 1, inset).

In 1959, Coover et al[2] discovered the adhesive properties of cyanoacrylate derivatives and suggested their use as surgical adhesives. Methyl-2-cyanoacrylate (Eastman 910 monomer) was the first cyanoacrylate derivative packaged and marketed as a surgical adhesive. This monomer is the shortest-chain derivative ($R = CH_3$, methyl). Longer-chain derivatives such as ethyl-2-cyanoacrylate (Krazy Glue), isobutyl-2-cyanoacrylate (Bucrylate), and butyl-2-cyanoacrylate (Histoacryl) have subsequently been developed. The primary concern with these compounds was the degree of histotoxic reaction associated with their use.

After numerous experimental studies it became apparent that the longer-chain cyanoacrylate derivatives ($R = C_4H_9$, isobutyl and butyl) were less toxic yet still had good adhesive properties.[3] In 1968, Tabb[4] used isobutyl-2-cyanoacrylate in the middle ear of guinea pigs and did not find any toxic reaction. For over a decade, neurosurgeons and neuroradiologists have been using isobutyl-2-cyanoacrylate on a clinical level as an embolic material for treatment of both extracranial and intracranial arteriovenous malformations. Then in 1971, Kerr and Smyth placed isobutyl-2-cyanoacrylate on the mucosa in the middle ears of cats and discovered a marked inflammatory response with damage to adjacent bone.[5] Kaufmann[6] used isobutyl-2-cyanoacrylate for tympanoplasties only to find similar histotoxic reaction of the middle ear despite the addition of topical steroids. In a recent study, Vinters et al[7] examined 17 intracranial arteriovenous malformations that were embolized using isobutyl-2-cyanoacrylate. The specimens were removed 5 days to 16 months after embolization therapy. There was evidence of patchy mural angionecrosis (adjacent to isobutyl-2-cyanoacrylate fragments), necrosis of parenchyma adjacent to embolized channels, and foreign body giant cells. In all specimens, isobutyl-2-cyanoacrylate was still present; however, there was evidence of partial degradation.

Leonard et al[3] thought that the longer-chain cyanoacrylate derivatives ($R = C_4H_9$, butyl) degrade at a slower rate, thereby permitting the degradation products to be more safely metabolized with evocation of a less intense inflammatory response. In 1968, Matsumoto et al[8] showed that n-butyl-cyanoacrylate had a much less intense inflammatory response when compared with methyl- and ethyl-cyanoacrylate.[8] Since that time, Histoacryl (butyl-2-cyanoacrylate made

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blue with 0.1% addition of 1-hydroxy-4-[-p-toluidion]-antrachion) was developed. This cyanoacrylate derivative has been used in Würzburg for middle ear surgery since 1969.[9] Smyth and Kerr[10] applied it to the middle ear in cats with only minimal tissue reaction. Seidentop,[11] in 1980, used Histoacryl in baboon ears with no evidence of significant tissue response. He concluded that Histoacryl was safe for human use. In 1984, Ronis et al[12] placed Histoacryl between two pieces of ear cartilage in four rabbits. Histologic examination of the specimens at 1, 2, 3, and 4 weeks revealed no evidence of cartilage necrosis or foreign body reaction.

Clinically, Histoacryl has been used in dentistry[13] and ophthalmology[14,15] without problems. Histoacryl has been used to aid in augmenting or reconstructing the nose.[16] In 1985, Sachs[17] reported his experience using Histoacryl in 39 cases for augmentation rhinoplasty. He found the adhesive to be reliable, easy to apply, and without systemic or local untoward effects. In a small series of 18 patients, Kosko[18] reported the use of Histoacryl for upper lid blepharoplasty. Kamer and Joseph[19] reported a series of 100 patients treated with Histoacryl on various surgical wounds (primarily blepharoplasty). They had no significant adverse effects with wound healing, graft rejection, or infection.

The Otorhinolaryngology Department of Temple University School of Medicine, Philadelphia, Pa, conducted a survey on the medical applications of Krazy Glue.[12] The survey was performed to determine the approximate number of institutions that use cyanoacrylate derivatives. Of the 115 departments polled, 56 replied to the survey. Of those that responded, 34% (19 departments) had a working knowledge of these adhesives. Despite our present knowledge of the significantly lower histotoxicity of Histoacryl, some surgeons continue to use shorter-chain derivatives such as ethyl-2-cyanoacrylate (Krazy Glue). In this long-term study, the histotoxicity of Krazy Glue will be compared with Histoacryl along with the ability of these compounds to bond cartilage and bone.

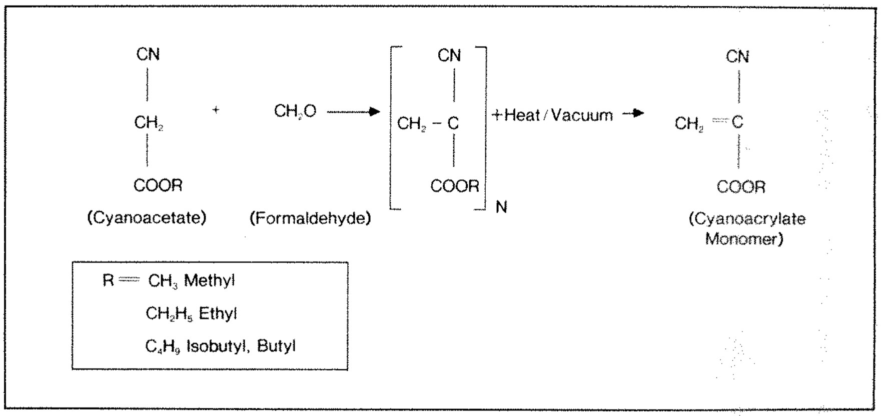

Fig 1.—Synthesis of cyanoacrylate monomers. Inset, Cyanoacrylate derivative changes as alkoxycarbonyl (—COOR) group is altered.

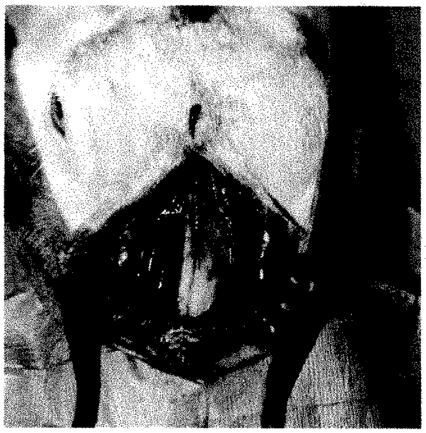

Fig 2.—Anterior wall of maxillary sinus removed and used as bone graft. Underlying mucosa of the sinus was left intact.

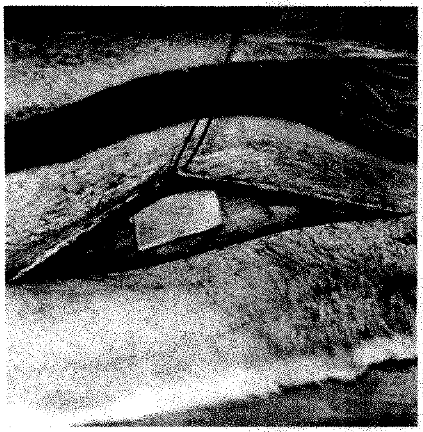

Fig 3.—Bone graft placed in pocket and glued to cartilage.

MATERIALS AND METHODS

Twenty adult white rabbits weighing between 2.5 and 3.5 kg were used in this study. All operations were performed using anesthesia by ketamine hydrochloride (30 mg/kg) and acepromazine maleate (1 mg/kg) administered intramuscularly. The fur was shaved off of the face and prepared with betadine solution. The ears were also prepared. The field was draped and the entire procedure performed under sterile conditions. A midline incision was made down the bridge of the nose through skin and periosteum. The periosteum was carefully elevated off the anterior wall of the maxillary sinus.

Using an osteotome, mallet, and elevator, a section of the roof or anterior wall of the maxillary sinus was removed, leaving the underlying mucosa intact (Fig 2). Then the edges of the periosteum were reapproximated with absorbable suture. The skin was closed in a continuous fashion with absorbable suture. The bone was cut in half and placed in sterile saline.

Then a 1.5-cm incision was made through skin and perichondrium on the ventral surface of the right ear. A small pocket was formed, and the bone graft was glued directly to the auricular cartilage (Fig 3) with a small drop of Krazy Glue. Enough glue was used to be sure a fine layer of adhesive was present between the entire bone graft and the auricular cartilage. Then the incision was closed with absorbable suture, and bacitracin ointment was applied.

The same procedure was performed on the left ear. However, Histoacryl was used to glue the bone graft to the auricular cartilage.

The operative sites were examined daily for 2 weeks, subsequently making less frequent inspections. The rabbits were monitored for dietary intake and activity and were weighed weekly to assess their general health.

Animals were killed at 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year. The last three rabbits were killed at 1 year. The

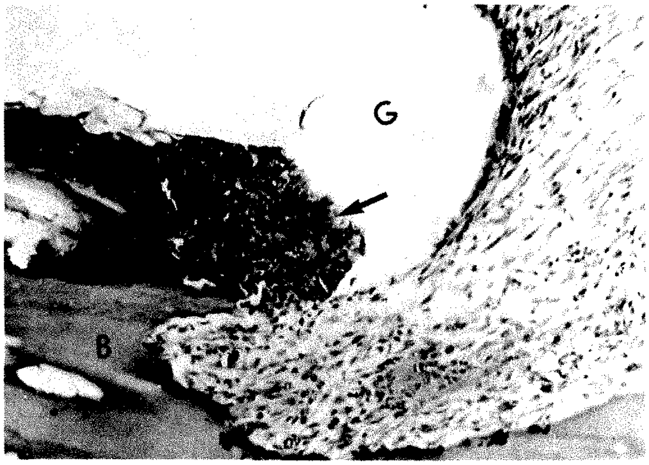

Fig 4.—Histologic examination at 1 week (hematoxylin-eosin, ×250). Ethyl ear. Acute inflammatory reaction with exudate and tissue necrosis. Arrow indicates acute inflammation; G, glue; and B, bone (necrotic).

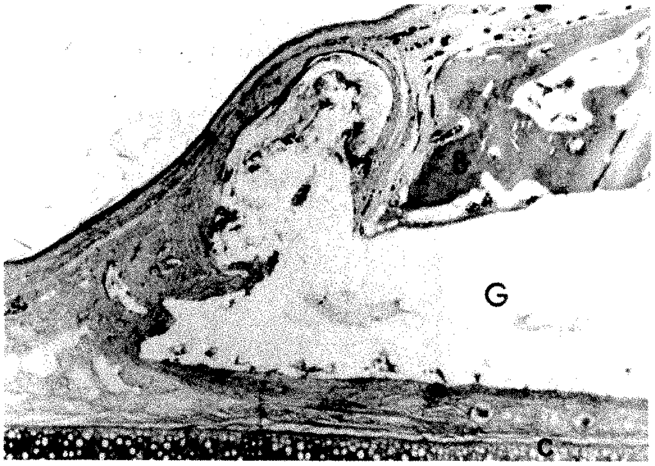

Fig 5.—Histologic examination at 1 week (hematoxylin-eosin, ×100). Butyl ear. Mild acute inflammatory reaction and mild foreign body giant cell reaction. No evidence of exudate or tissue necrosis. G indicates glue; B, bone; and C, cartilage.

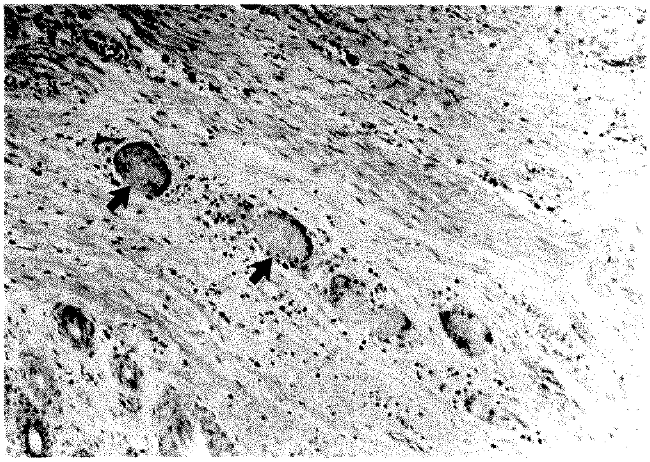

Fig 6.—Histologic examination at 1 month (hematoxylin-eosin, ×250). Ethyl ear. Mild foreign body giant cell reaction with no acute inflammation. Arrows indicate multinucleated giant cells.

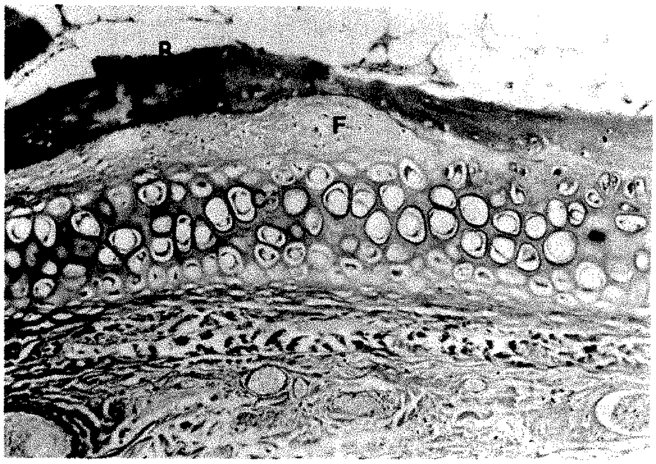

Fig 7.—Histologic examination at 1 year (hematoxylin-eosin, ×100). Ethyl ear. Complete degradation of polymer with fibrosis and viable bone graft. B indicates bone; C, cartilage; and F, fibrosis.

rabbits were killed using an intravenous injection of euthanasia solution. The ears were harvested and submitted in 10% formaldehyde solution. All specimens were decalcified. The slides were stained using hematoxylin-eosin, and a special oil red O stain was used to aid in visualizing the cyanoacrylate polymer.[20]

RESULTS

The rabbit ears were inspected carefully to monitor for inflammation, infection, or graft rejection. Data were recorded according to animal number and whether it was the right or left ear. Right ears were those in which Krazy Glue (ethyl-2-cyanoacrylate) was used to secure the bone graft and will hereafter be referred to as "ethyl" ears. Left ears were those in which Histoacryl (butyl-2-cyanoacrylate) was used to secure the graft and will hereafter be called "butyl" ears.

During the first week, 9 of 20 of the ethyl ears developed sterile fluid collections (serosanguineous fluid that was culture negative) that had to be aspirated on at least one occasion. In 2 ethyl ears, the fluid had to be drained daily for 10 and 11 days, respectively. In 5 ethyl ears there was partial necrosis of the perichondrial flap, resulting in graft exposure. In 3 of these ears the graft was extruded. At 1 week, histologic examination of the ethyl ears revealed a severe acute inflammatory reaction with neutrophils, exudate, and necrotic bone (Fig 4).

Only 1 of 20 butyl ears developed a small sterile fluid collection that quickly cleared up after aspirating the fluid. At 1 week, histologic examination of the butyl ears showed a mild acute inflammatory reaction and a mild foreign body giant cell response with no evidence of tissue necrosis (Fig 5). In a few specimens, a small amount of polymer leaked out from between the bone grafts and cartilage eliciting a more intense inflammatory response where the glue contacted surrounding soft tissue.

At 2 weeks, the ethyl ears had a less intense acute inflammatory reaction with an intensifying foreign body gi-

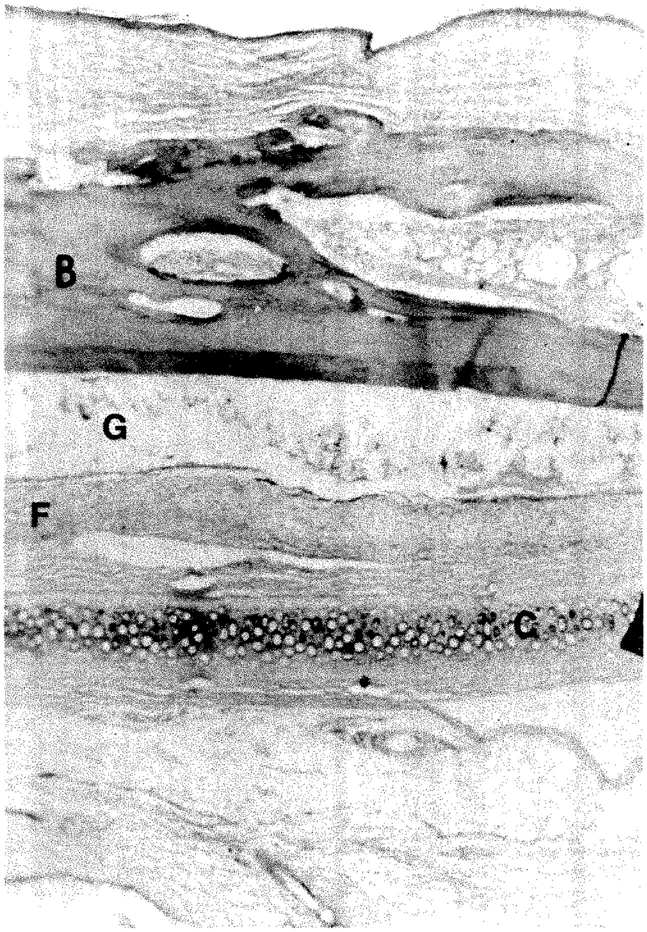

Fig 8.—Histologic examination at 1 year (hematoxylin-eosin, ×40). Butyl ear. Some residual polymer with viable bone graft. B indicates bone; C, cartilage; F, fibrosis; and G, glue.

ant cell reaction. Histiocytes were pallisading around the polymer and some glue was noted in the cytoplasm of the histiocytes. The butyl ears demonstrated a relatively mild foreign body giant cell reaction with no acute inflammatory reaction. The histologic appearance of the butyl ears essentially stabilized after 2 to 4 weeks.

At 1 month, the ethyl ears showed decreased acute inflammation and primarily a foreign body giant cell reaction with inclusions of adhesive material (Fig 6). There also was a decrease in the amount of adhesive material present in the wound. The butyl ears had viable bone with minimal foreign body giant cell reaction. There was much less tissue reaction in the butyl ears as compared with the ethyl ears.

At 3 months, the ethyl ears showed viable bone grafts and decreased acute inflammation, and a foreign body giant cell reaction persisted. There was increased fibrosis that appeared to be replacing the polymer as it degraded. In some specimens there was dead bone surrounded by fibrosis and scar. The butyl ear showed only rare foreign body giant cells and slow degradation of the polymer with minimal fibrosis. At 6 months, the ethyl ear showed more fibrosis with a mild foreign body giant cell reaction and almost complete degradation of the adhesive. The butyl ear showed some degradation of the polymer with rare foreign body giant cells. There was less fibrosis and scar in the butyl ear.

At 1 year, the ethyl ear showed complete degradation of the polymer and fibrosis (Fig 7). The butyl ear showed some persistent adhesive with rare foreign body giant cells and fibrosis (Fig 8). The viable bone graft was revascularized and incorporated into the host site, stabilized to adjacent cartilage.

After a 1-year follow-up there was no evidence of carcinogenesis despite the prolonged presence of the Histoacryl adhesive polymer.

COMMENT

The clinician's primary concern with the use of cyanoacrylate derivatives lies in their toxicity. The longer-chain derivatives (higher homologues) such as isobutyl-2-cyanoacrylate and, particularly, Histoacryl (butyl-2-cyanoacrylate) have the least histotoxic effects. This study demonstrated that Krazy Glue (ethyl-2-cyanoacrylate) produces a sizeable acute inflammatory response with a persistent foreign body giant cell reaction. Even though this cyanoacrylate derivative degrades relatively rapidly, the histotoxic effects can result in complications such as tissue necrosis, graft rejection, sterile abscess formation, persistent edema, and extensive fibrosis.

By tagging methyl-, n-butyl-, and n-heptyl-α-cyanoacrylate with carbon 14, Ousterhout et al[21] demonstrated in rats that there was absorption of these substances from skin and donor graft sites, proved by radioactivity in the urine. They showed that the urinary ^{14}C activity was directly related to chain length, with the methyl derivative having the greatest urinary ^{14}C. This is consistent with the known fact that the higher homologues degrade more slowly than the lower homologues. The rapid degradation of the lower homologues (methyl- and ethyl-2-cyanoacrylate) may release relatively large quantities of toxic byproducts such as cyanoacetate and formaldehyde.[22] These toxic materials could elicit the acute inflammatory response noted with the shorter-chain derivatives. Long-chain derivatives degrade at a slow rate, releasing small quantities of toxic by-products. The host tissue may be able to handle small amounts of these toxins, explaining the minimal inflammatory response associated with the higher homologues.

When using cyanoacrylates, small quantities should be used because with larger quantities the cumulative heat dissipated during polymerization can produce tissue damage. The heat dissipated also depends on the monomer. A mean temperature rise of 4°C was recorded for methyl-2-cyanoacrylate and a net rise of 1.5°C was recorded for butyl-2-cyanoacrylate.[23]

The development of sarcomas in rats

after subcutaneous injection of large doses of methyl monomer is the only link of these compounds to carcinogenesis.[24] Methyl-2-cyanoacrylate was subsequently banned by the Food and Drug Administration for human use. Some investigators believe these data represent the Oppenheimer effect, or that this is a dose-related effect not specific for the substance investigated.[25] Further studies have failed to show carcinogenesis with isobutyl- and butyl-2-cyanoacrylate.[26-28] One advantage of ethyl-2-cyanoacrylate is its relatively rapid degradation (within 12 months). The prolonged tissue exposure of the butyl-2-cyanoacrylate adhesive raises further questions about its long-term effects.

Histoacryl works well for binding bone to cartilage or cartilage to cartilage.[12] Graft survival is high with minimal inflammation and no tissue-graft necrosis. Initially, two pilot rabbits were used, implanting only bone (no glue) into both ears to evaluate the effectiveness of this model. The pilot rabbits were killed at 1 and 2 weeks. Both did well. Histologic examination revealed mild inflammation at 1 week, which eventually resolved at 2 weeks. Even though the butyl ears showed minimal inflammation, it was greater than that seen in the pilot rabbits. Therefore, Histoacryl elicits less inflammation than Krazy Glue but more inflammation than a baseline bone homograft with no glue. Ideally, when using this adhesive, very small quantities of Histoacryl should be used to stabilize just a segment of the graft to allow rapid revascularization of the region of graft not in contact with the glue.

Histoacryl appears to be the least histotoxic of the cyanoacrylate derivatives. The adhesive is relatively nonreactive, easily applicable, and reliable, has good bonding strength, and is relatively inexpensive. When used in small quantities between poorly vascularized tissues such as bone and cartilage, this adhesive is safe with minimal inflammation. However, there appeared to be increased inflammation where Histoacryl leaked out from between bone graft and cartilage to contact well-vascularized soft tissue. Future studies will evaluate the histotoxic reactivity of Histoacryl when contacting well-vascularized subcutaneous tissues.

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Comparison of Biomaterials for Facial Bone Augmentation

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• We compared the gross behavior of and microscopic response to implant materials currently in clinical use for facial bone augmentation at different sites in dogs. Materials evaluated include porous polytetrafluoroethylene carbon (Proplast), large-pore high-density polyethylene (Medpor), solid medical-grade silicone rubber (Silastic), polyamide mesh (Supramid), and autogenous rib bone. The subjects were 12 mixed-breed dogs and the materials were implanted directly on bone with periosteum removed at one of three sites in the dog's face (malar eminence, nasal dorsum, and chin). Animals were killed 3 months after surgery and stability of the implants was graded by manual manipulation. Blocks of tissue, including the study materials and underlying bone, were examined microscopically after sectioning. Stability results are tabulated and histologic appearance is described by site for each material evaluated. These data demonstrate marked variability of stability and cellular response depending on the *site* of implantation. From these data one may conclude that the site of implantation and implant movement are essential factors in determining the nature of the tissue response and fate of an implant. Solid and porous alloplastic materials show an acceptable tissue response, but neither demonstrates the ability to consistently provide an implant that is stable on underlying bone.

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Deformity of the facial skeleton has many causes: trauma, congenital deformities, or malignancies. Many surgical procedures have been devised to restore facial contour, and implantable materials are being used with increasing frequency for restoration of facial skeletal defects. Correction of tip and saddle deformities and reconstruction of alar or septal defects are common uses of implant materials in the nose. Restoration of facial skeletal contour after trauma, maxillectomy, or craniofacial anomalies resulting from congenital disorders such as Treacher Collins syndrome and Crouzons disease exemplify other uses for midface implants. Augmentation of the malar eminence and mentum are now widely performed cosmetic surgical procedures.

The facial sites where implants are most commonly employed are the nasal dorsum, chin, and malar eminence. Table 1 provides a perspective on the relative frequency with which implants are used at particular sites in the face.

The choice of implant materials remains an issue of challenge and contention. Autogenous tissue has been to date the standard with which synthetic materials have been compared. Autogenous tissue offers the advantages of tissue compatibility that even "inert" synthetics cannot.

Early reports of the use of autogenous tissue implants in facial reconstruction from the late 19th and early 20th centuries showed favorable results. Israel[1] described the use of tibial bone transplants for nasal reconstruction in 1896 and his work was later adopted by Joseph[2] and others. Von Mangold[3] reported the use of costal cartilage in 1900 and set the stage for extensive experience with and current use of this tissue.

Later reports described variable resorption and/or remodeling of autogenous bone and cartilage grafts in clinical and experimental settings.[4,5] In 1950, Mowlem[6] described the use of overlay bone graft for restoring facial contour, which survived initially but later displayed varying degrees of resorption and shrinkage. He concluded that in the absence of mechanical stress that the bone is designed to

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Table 1.—Sites of Facial Bone Augmentation

- Nasal defects (45%)
  - Trauma
    - Inadequate reduction of fracture
    - Septal hematoma (saddle deformity)
    - Deformity secondary to rhinoplasty
  - Infection
    - Septal abscess (saddle deformity)
  - Neoplasm
  - Loss of tip support
- Mentum defects (20%)
  - Cosmetic mentoplasty
- Malar eminence defect (15)
  - Congenital
    - Cosmetic augmentation
    - Maxillary hypoplasia (Crouzon's disease, Treacher Collins syndrome, etc)
  - Trauma
    - Inadequate reduction of fracture
    - Surgical resection of tumor
- Frontal bone defect (10%)
  - Trauma
  - Infection
- Others (10%)
  - Submalar augmentation, orbital and auricular reconstruction,etc

Table 2.—Materials Used

- Proplast (porous polytetrafluoroethylene and pyrolyzed carbon
- Medpor (porous polyethylene)
- Supramid (woven polyamide mesh)
- Silastic (silicone rubber)
- Autogenous rib

withstand, variable resorption and remodeling will occur.

More recently, several reports have demonstrated increased survival and viability with the use of membranous (vs endochondral) bone grafts and, in particular, vascularized calvarial bone grafts.[7-11]

Along with the inherent quality of tissue compatibility, however, it is well to consider the disadvantages of autogenous tissue, which include (1) restricted availability of donor tissue; (2) harvesting the autograft, which exposes the patient to risks of a second surgical procedure that can virtually dwarf the reconstructive surgery; (3) graft resorption or shrinkage; and (4) unpredictable remodeling of the implant. Irradiated homologous tissue has demonstrated similar shortcomings of resorption and shrinkage.[12]

Attempts to circumvent the apparent disadvantages of autogenous tissue implants led to the use and development of a plethora of naturally occurring and synthetic substances for facial implantation. Early reports favored heavy metals such as gold, silver, and platinum.[13,14] Roussett described the versatility of facial contouring achievable by shaping gold or silver implants for the nose in 1828, and others espoused various metals such as lead or aluminum as being ideal materials.[13] Ellison[15] was among the first to report extrusion of an implant in 1894. Gersuny[16] and others described the use of injectable materials such as low-melting-point paraffin at the turn of the century. These techniques were later abandoned after severe local reactions and embolic complications were experienced.[13]

In the late 1930s, with the introduction of the "new plastics," extensive research and development for use of alloplastic materials for human implantation exploded. By the late 1950s many laboratory and clinical studies were appearing in the literature with various formulations of silicones, polyamides, methacrylates, and other polymers. LaVern and Baberio[17] published a comprehensive report on tissue reaction to polytetrafluoroethylene (Teflon) in 1949. The low tissue reactivity, absence of toxicity, and nonallergic properties of silicone were well documented by Brown et al[18] and Marzoni et al,[19] and were reviewed by Zarem.[20] A number of authors have reported their experience with particular biomaterials: Stucker et al[21,22] and Beekhuis[23,24] with polyamide mesh (Supramid), Parkes and Kamer[25] and Epstein[26] with porous polytetrafluoroethylene (Proplast), and Rubin[27] with high-density porous polyethylene (Medpor).

Many articles have cited individual biomaterials as being ideal for use in facial contouring, but few have compared the currently used materials in a single model at the common sites of facial implantation.

Our purpose was to compare the materials in current clinical use by assessing stability in the usual sites of implantation and the tissue response in a dog model.

MATERIALS AND METHODS

The subjects chosen for this study were 12 mixed-breed dogs weighing between 12 and 20 kg. These animals were chosen for two reasons: (1) Merwin et al[28] were successful using this model, and (2) the size and architecture of the dog skull is suitable for implantation of materials approximating the size contoured for use in humans.

Materials evaluated in this study were chosen based on their frequency of use in human implantation and are listed in Table 2. Implant size was determined by fashioning clay molds on a preserved dog skull.

Using a sterile technique, 5-cm sections of fourth or fifth rib were harvested and subsequently bisected and shaped using a rotary drill burr for immediate implantation in the same animal. Segments 2.5 cm long (for nasal dorsum) and 1.5 cm long (for malar eminence) were cut and placed in sterile saline solution until implanted.

Proplast is porous black pyrolyzed carbon and polytetrafluoroethylene with a pore size of 80 to 400 μm. It is supplied in prepackaged blocks ready for autoclaving and is easily shaped using a sharp scalpel. It has a feltlike texture with pores that are easily crushed unless the material is handled carefully. These implants were carved, rinsed in sterile water, and autoclaved before implantation.

Medpor is white ultra-high-density porous polyethylene. Its large pore size (125 to 250 μm) is reportedly suitable for bone ingrowth.[29] It is a hard substance that is contoured using a sharp scalpel and is supplied in sterile prepackaged blocks measuring 38 × 63 × 6.5 mm with prohibition on resterilization. Implants were shaped under sterile conditions during surgery.

Supramid is white woven polyamide mesh. It is shaped by folding or rolling the material and sutured to retain the desired shape (according to the method of Stucker[21]) and is supplied in prepackaged sheets measuring 30 cm^2.

Silastic is solid medical-grade silicone rubber and is available in soft, medium, and firm consistencies. It is easily contoured using a sharp blade and is supplied in prepackaged blocks ready for autoclaving. This material was carved, rinsed, and autoclaved prior to implantation.

Sites of implantation were chosen based on the frequency of implantation in humans (Table 1) and the materials implanted at these sites were chosen based on their pattern of clinical usage. Acutely harvested rib and alloplastic materials were contoured for the specific site and implanted directly on bone, with periosteum removed, at three sites in the dogs (Fig 1) as previously described by Merwin et al.[28]

Postoperative evaluation included examination for signs of infection or hematoma or seroma formation at both the implant site and rib harvest site, and manual evaluation of implant stability. Animals were

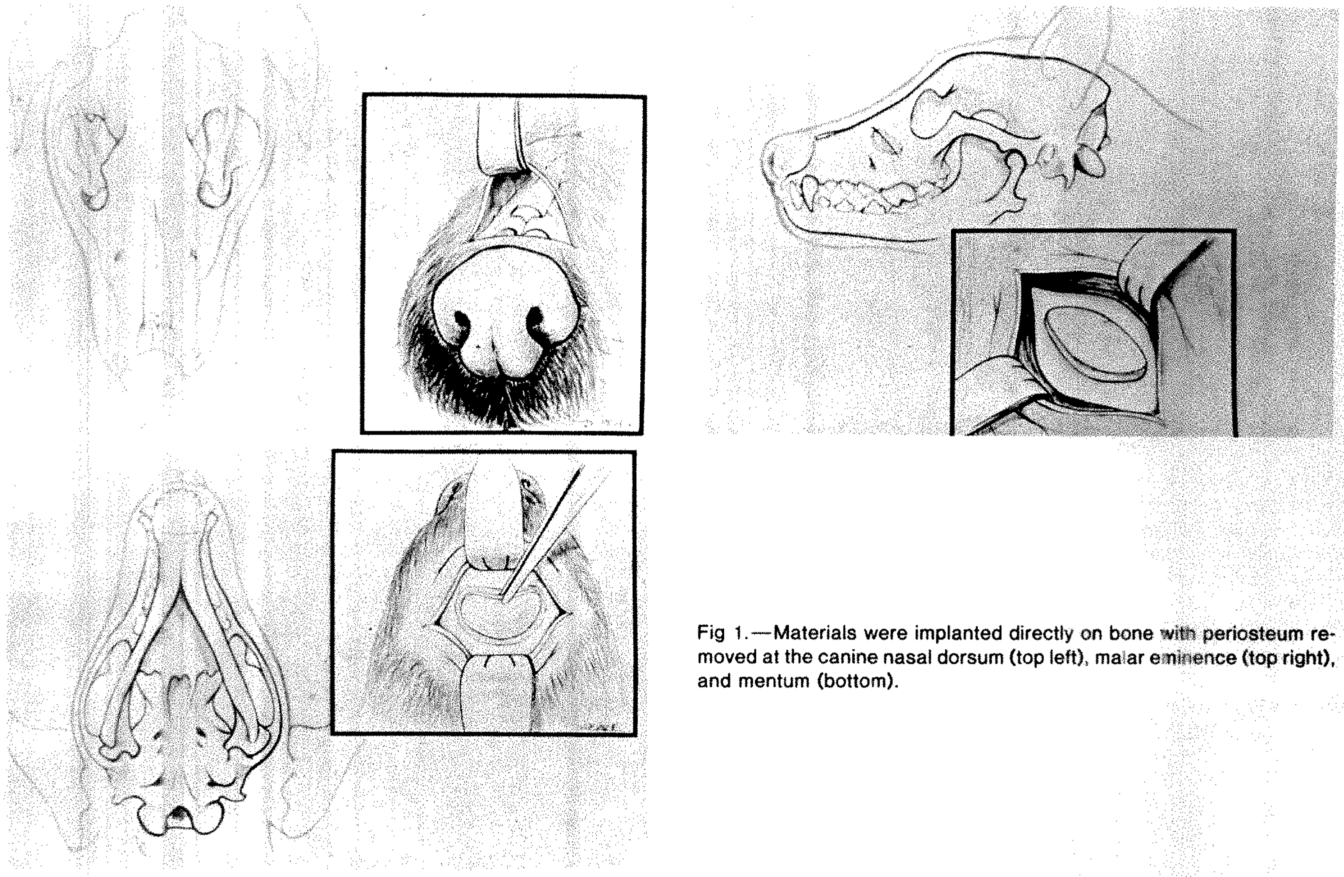

Fig 1.—Materials were implanted directly on bone with periosteum removed at the canine nasal dorsum (top left), malar eminence (top right), and mentum (bottom).

killed 3 months after implantation, and data obtained at necropsy included gross tissue reaction and stability of implants graded by manual manipulation. Tissue specimens including implant materials and underlying bone were removed en bloc at autopsy for microscopic evaluation of tissue response. Results of manual testing for stability were graded categorically as defined in Table 3.

Table 3.—Implant Stability Grading

Grade	Criteria
Bone bond	Implant rigid on bone
Soft-tissue bond	Implant adherent in soft tissue
No bond	No tissue adhesion to implant
Lost	Implant missing at autopsy

Table 4.—Stability Results by Site*

	Bone Bond	Soft-Tissue Bond	No Bond	Lost
Malar				
Proplast	2	4	0	0
Medpor	4	2	0	0
Silastic	0	6	0	0
Rib	0	0	0	6
Nose				
Supramid	2	4	0	0
Rib	5	1	0	0
Chin				
Proplast	0	0	6	0
Silastic	0	0	6	0

*In numbers of cases.

RESULTS

Stability results by site show the number of dogs displaying the defined stability grading by manual manipulation for each implant.

At malar sites (Table 4), two Proplast implants were stable on underlying bone and four were stable within soft tissue. Medpor demonstrated the best results at this site, with four stable on underlying bone and two stable within soft tissue. All Silastic implants were stable within soft tissue and all rib implants were resorbed and not found at autopsy. At the nasal dorsum (Table 4), rib implants fared significantly better, with five of six implants stable on underlying bone. Supramid implants demonstrated two stable on underlying bone and four stable within soft tissue. No implants were lost or resorbed at this site. Silastic and Proplast chin implants (Table 4) demonstrated no appreciable stability. All implants were freely mobile within soft tissue and were thus graded as "no bond." No implants were lost or extruded at this site.

Although rib implants at the malar prominence were completely resorbed and not found at necropsy, the tissue response to rib at the nasal dorsum was characterized by vascularized fibrous tissue ingrowth and minimal bone revitalization (Fig 2). There was demonstrable predominance of nonrevitalized bone even 3 months after implantation.

The tissue response to Proplast was characterized by fibrous tissue ingrowth throughout this porous material (Fig 3). There was marked breakup and migration of scraps of this mate-

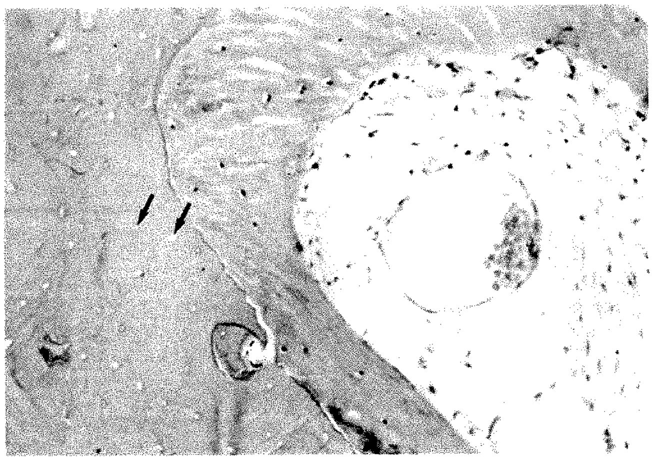

Fig 2.—Section of autogenous rib implant at the nasal dorsum demonstrates vascularized fibrous tissue growth into a bony trabeculae and minimal bone revitalization even 3 months after implantation. Note the predominance of nonrevitalized bone evidenced by empty lacunae (arrows) (hematoxylin-eosin, ×200).

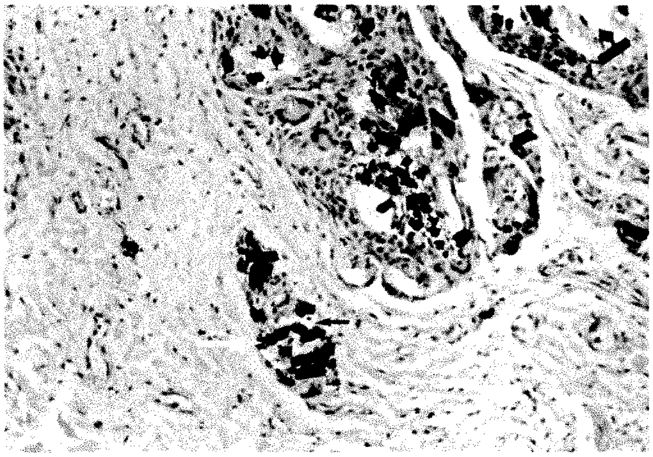

Fig 3.—Proplast implant under polarized light demonstrates extensive fibrous tissue ingrowth. Breakup and migration of fragments of the implant material is evident, with a significant cellular response including macrophages and multinucleated giant cells. Refractile and black fragments represent the polytetrafluorcethylene (white arrow) and pyrolyzed carbon (black arrow) components of the material, respectively (hematoxylin-eosin, ×200).

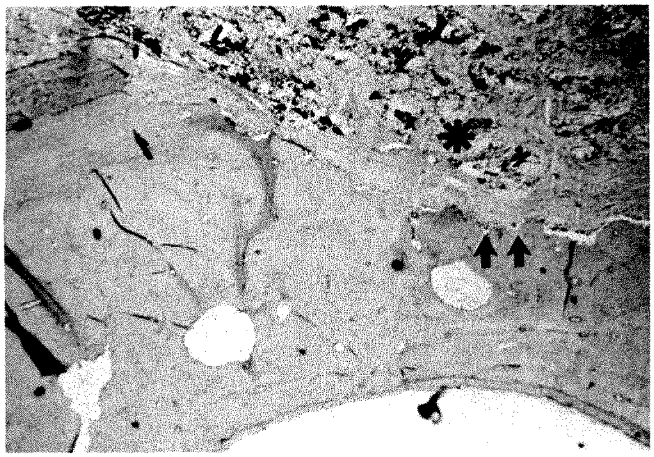

Fig 4.—Section through Supramid implant (asterisk) at bone-implant interface. Extensive fibrous tissue ingrowth is seen. Note the "bitten away" appearance of the underlying bone (arrows), evidence of resorption (hematoxylin-eosin, ×40).

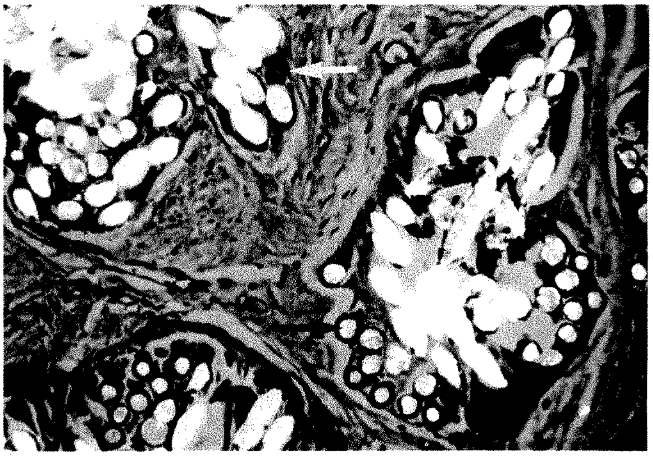

Fig 5.—Detail of Fig 4 under polarized light demonstrates the microstructure of the material: polyamide filaments (black arrow) are twisted to form threads that are woven into fabric. Vascularized fibrous tissue ingrowth is evident, but note the significant cellular response between the filaments (within the threads), including multinucleated giant cells (white arrow) (hematoxylin-eosin, ×200).

rial that were surrounded by a large number of inflammatory cells, including phagocytes and multinucleated giant cells, implying a continued stimulus for active cellular response and giant cell formation even after 3 months. No bone had grown into the implants and erosion of underlying bone was noted in two cases. At the chin all implants were mobile and demonstrated significant scarring.

Supramid mesh micrographs characterized both the microstructure and the tissue response to this material (Figs 4 and 5). Polyamide filaments are twisted to form threads, which are subsequently woven into fabric. Between the threads there is thick acellular fibrous tissue ingrowth, which is the desired response to this material. However, within the threads and between filaments, an inflammatory response, including multinucleated giant cells, was observed.

Malar Silastic implants were contained in a thin, relatively acellular nonadherent capsule with no inflammation (Fig 6). Osteoclast activity was noted in two cases and in one, bone was present at the interface. At chin sites, the capsules were much thicker, with scarring and evidence of delayed healing.

Medpor implants demonstrated acellular fibrous tissue ingrowth throughout this porous material, with occasional giant cells (Fig 7). These cells were particularly noted at the tissue-implant interface. Although the

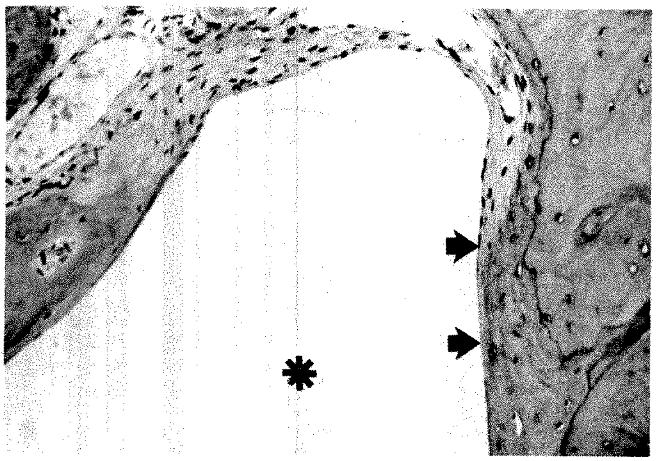

Fig 6.—Silicone implant shows intimate apposition of the implant (asterisk) and underlying bone (arrows) with a thin acellular capsule. No "bonding" is evident, however, as these implants were freely mobile (hematoxylin-eosin, ×100).

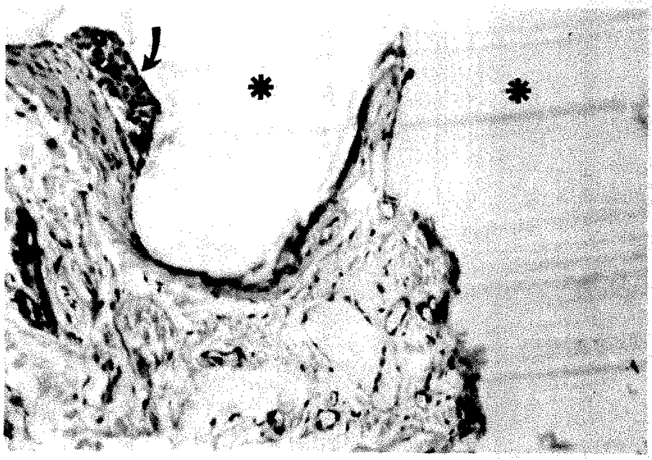

Fig 7.—Medpor implant under polarized light demonstrates the porous material (asterisks) with fibrous tissue ingrowth into a large pore (white arrow). Note the active cellular response at the tissue-implant interface, including a multinucleated giant cell (black arrow). The stimulus for this response may be relative movement at the interface and/or the configuration of the material (hematoxylin-eosin, ×200).

pore size (125 to 200 μm) of this material is reportedly suitable for bone ingrowth, none was observed in this study.

COMMENT

The results of mobility testing clearly show that porous materials will not necessarily provide an implant that is stable on bone. Of the 24 porous materials implanted, only 6 were stable on underlying bone at 3 months. With Supramid, the presence of giant cells within the threads implies that stress on the fabric causes movement between the filaments, damaging ingrown tissue, which is probably the stimulus for giant cell formation. Mobile Proplast implants displayed surrounding scar tissue with breakup and migration of the implant. Macrophages and giant cells at the sites of distant fragments of implant suggest that the size and/or configuration of these fragments generate this response. While Medpor implants showed the greatest stability, with 4 of 6 stable on bone, relative movement of tissue within some pores did give rise to a phagocytic response, although much less than was seen with other materials. Supramid, Medpor, and Proplast all demonstrated reactive cellular responses at 3 months, and this continuing cellular activity, however generated, is a mark of instability.

Because the synthetic materials studied are designed to be kept in place by connective tissue ingrowth and do not bond directly to tissue, *relative movement* at the interface is unavoidable. This movement contributes to the production of the cellular responses described in this study, which may tend to make the implant unstable in the long term. Thus, at *malar* sites, providing an architecture that confers increased mobility, rib implants were completely resorbed, whereas the more stable situation with rib implants on the *nasal dorsum* showed not only the presence of the implant, but five of six stable on bone. Similarly, at the chin, where by virtue of its architecture, relative movement is unavoidable, implanted materials fared poorly. Movement of the implant is an essential factor in determining the nature of the tissue response and the eventual success of an implant.

Finally, we conclude that the individual materials in this study will demonstrate a variable tissue response depending on the site of implantation and that none will consistently provide a bonelike stability on underlying bone. The disproportionately poor results for all materials implanted at the chin relative to the results at other sites, and similar data obtained in a previous study, suggest that the dog chin is a poor model for evaluation of implants.[28]

Current and future considerations in facial bone augmentation should include the potential usefulness of the "selectively bioactive" materials and substances that promote implant stabilization. Bioglass (bioactive glass, University of Florida, Gainesville) has demonstrated ability to form physiochemical bonds with bone, which eliminates the need for fibrous tissue ingrowth for stabilization.[28,30] IP200 and IP500 (Interpore International, Irvine, Calif) are porous hydroxyapatite materials produced by and obtained from the coral genera *Porites* and *Goniopora*, respectively. These porous materials have biologic properties that have been shown experimentally to *induce* bony ingrowth.[31]

The experimental and theoretical uses of tissue proteins termed *skeletal growth factors* that exhibit *osteoproductive* and *osteoinductive* properties have been recently described, and their clinical applications are on the immediate horizon.[32,33]

The need for careful scientific evaluation of these newer substances, in both experimental and clinical settings, as well as analysis of the long-term results of the materials in current clinical use is apparent. Recent data derived from rodent studies have suggested there may be a cancer risk associated with silicone implants.[34] This phenomenon is considered by most experts to be particular to rodents and should not be extrapolated to humans. Nevertheless, it brings to light questions about tissue responses to even the more commonly used implant material. Surgeons with extensive experience in the use of polyamide mesh have recently reported that late resorption and loss of facial contour may occur with use of this material (Colton J, Beekhuis J. 1989. Unpublished findings).

Technical advances in biomaterials and their utilization, widespread use of the various implantable materials, and new findings concerning the properties and fate of "established" implant materials dictate the need for the continued evaluation of these materials clinically and experimentally.

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ARCHIVES OF SURGERY

Ongoing 'Threats' to Biliary Surgery

Avram M. Cooperman, MD; Jerome Siegel, MD; Hillel Hammerman, MD; Richard Neff, MD (*Arch Surg.* 1989;124:1368)

Oxygen Delivery in Patients With Adult Respiratory Distress Syndrome Who Undergo Surgery: Correlation With Multiple-System Organ Failure

H. Gill Cryer, MD, PhD; J. David Richardson, MD; Sarah Longmire-Cook, MD; C. Matthew Brown, MD (*Arch Surg.* 1989;124:1378-1385)

Current Results of Treatment for Distant Metastatic Well-Differentiated Thyroid Carcinoma

William J. Wood, Jr, MD; S. Eva Singletary, MD; Robert C. Hickey, MD (*Arch Surg.* 1989;124:1374-1377)

Topical and Oral Treatment of Chronic Otitis Media With Ciprofloxacin

A Preliminary Study

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• The clinical and bacteriological efficacy of ciprofloxacin was studied in three groups composed of 20 patients each, all of whom were affected by chronic otitis media in the acute stage. Ciprofloxacin was randomly administered according to the following schedules for 5 to 10 days: 250 mg orally twice a day (group A); 3 drops (250 μg/mL in saline solution) locally twice a day (group B); and both of the previous treatments twice a day (group C). A high percentage of favorable clinical response (100% and 95%) and bacteriological eradication (95% and 85%) was observed in groups B and C. A low percentage of patients (65% and 40%) were clinically and bacteriologically cured by the oral therapy (group A). No worsening of the audiometric and vestibular function was observed after local therapy. The results of this preliminary study suggest that the use of topical ciprofloxacin is effective in curing chronic otitis media, even when it is caused by *Pseudomonas* (47% of the total bacterial detections).

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Suppurative processes characterized by purulent otorrhea are very frequently and recurrently observed in patients affected by chronic otitis media (COM), and bacterial responsibility in these processes is certain.

Gram-positive and gram-negative aerobic, as well as anaerobic, bacteria are in fact involved in the etiology of suppurative COM, with different incidence.[1-4] The frequent detection of *Pseudomonas* and other multiresistant bacteria and the possible low concentrations of antibiotics in the middle ear are probably responsible for the frequent failures following empirical therapy with conventional antibacterial agents. To date, the epidemiological findings in suppurative otitis frequently suggest treatment with antibiotics that also include *Pseudomonas* in their antibacterial spectrum, such as aminoglycosides. However, these antibiotics cannot be recommended, especially for local instillation, because of the high risk of ototoxicity.[5-7]

The aim of the present preliminary study was to evaluate the therapeutic efficacy and tolerability of ciprofloxacin, which is a particularly active nontoxic drug against *Pseudomonas*, orally or topically administered in the treatment of COM in the acute stage.

PATIENTS AND METHODS

Patients

Sixty adult patients (31 men, 29 women) affected by suppurative COM were included in the study. Data concerning the patients' demographic characteristics are reported in Table 1. All patients were affected by mild or moderate COM in the acute stage without cholesteatoma or mastoiditis.

Table 1.—Patients' Demographic Characteristics

	Sex		
Group	**M**	**F**	**Mean Age, y**
A	9	11	36
B	12	8	39
C	10	10	40
Total	**31**	**29**	**38**

Table 2.—Prior Therapies

Drugs	**No. of Patients**
Cephalosporins	13
Lincomycin	6
Penicillins	5
Tetracycline	2
Neomycin/colistin sulfate*	7
Others†	5
Total	**38 (63%)**

*Local drops.

†Gentamicin, netilmicin sulfate, erythromycin, miokamycin, and sulfamethoxazole/trimethoprim.

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Pregnant women, patients with a history of previous allergy to quinolone derivatives, and patients younger than 18 years were excluded. All patients had given their informed consent before entering the study. No patient had any underlying diseases (such as diabetes), and none was taking any other drug during the study. Many of the patients (38 [63%] of 60) had been taking different systemic and local antibiotics at appropriate dosages for at least 5 days before beginning the new therapy, without any significant improvement of the subjective symptoms (Table 2).

Antibiotic Treatments

Ciprofloxacin was randomly administered according to the following schedules: group A (20 patients), 250 mg orally twice a day; group B (20 patients), 3 drops containing 250 μg/mL of ciprofloxacin in saline solution locally twice a day; and group C (20 patients), both the previous treatments twice a day.

Ciprofloxacin solutions were prepared by dissolving the pure sterile ciprofloxacin powder in saline solution to obtain the final concentration of 250 μg/mL. Preliminary studies were performed using an agar diffusion method to evaluate a possible loss of activity of the solution stored either in the refrigerator or at room temperature. These tests were carried out for 10 days and did not show any decrease of the in vitro antibacterial activity of the drug.

Patients' Examination

Patients were clinically examined before, during (every 2 to 3 days), and after the end of the therapy, and an accurate inquiry for side effects was carried out at each clinical control. Audiometric measurement and vestibular tests were performed before and 24 hours after the end of the therapy in patients receiving topical treatment only.

Aerobic cultures of the middle ear effusions were always performed before the beginning of the therapy and, if the secretion was still present, at each clinical control. All bacteria were identified by the API system (Bio-Herieux). Susceptibility to ciprofloxacin was studied by determining the minimal inhibitory concentrations by a microdilution broth method.

Treatments were carried out for at least 5 days. Patients who were not cured after this period of therapy continued the treatment until cure, or, in any case, not longer than 10 days. The clinical and bacteriological evaluation was stated 24 hours and 14 days (follow-up) after the interruption of treatment.

Statistical Analysis

χ^2 was calculated to compare the percentages of clinical and bacteriological responses in the three groups of patients examined, to evaluate a possible statistical difference.

RESULTS

Data concerning the isolation of the responsible bacteria from the middle ear effusion are reported in Table 3. We detected a single responsible bacteria in all cultures except one from one patient in group B. This patient had a mixed culture consisting of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The distribution of bacteria was homogeneous, especially in groups B and C. Group A had a higher prevalence of *Pseudomonas* (60%); consequently, the number of gram-positive cocci detected was lower, (25%). Clinical and bacteriological responses are reported in Tables 4 and 5, respectively.

In group A, 13 (65%) of the 20 patients had a favorable clinical response to the oral ciprofloxacin therapy and 7 (35%) showed no significant clinical improvement. These results corresponded to a high percentage of bacteriological persistence or superinfection.

Of the 20 patients in group B, who received only locally administered drops of ciprofloxacin, a clinical cure was observed in 17 (85%) and improvement was noted in 3 (15%). Two of the patients who were clinically improved still had a very small ear secretion, which was sterile, and one was still infected by *Escherichia coli*.

Of the 20 patients in group C, who received both oral and topical ciprofloxacin, 15 (75%) were clinically cured, 4 improved, and 1 failed. In two patients with significant clinical improvement, there was persistence of a very small ear effusion, which was bacteriologically sterile. In two other patients, we observed a remarkable clinical improvement with a significant decrease of the ear effusion, which was still infected by *S aureus* and *P aeruginosa* in one and superinfected by *S aureus* in the other. Finally, one patient was not clinically or bacteriologically cured, as there was persistence of *S aureus* in the culture of his middle ear effusion. Bacteria isolated from the cultures after the end of the treatment are reported for each patient group in Table 6.

Table 3.—Responsible Bacteria Isolated Before Treatment

	Group, No. (%)			
	A	B	C	Total
*Pseudomonas**	12 (60)	8 (38)	8 (49)	**28** (46)
Gram-positive cocci†	5 (25)	10 (48)	9 (45)	**24** (39)
Enterobacteria‡	3 (15)	3 (14)	3 (15)	**9** (15)
Total	**20**	**21**	**20**	**61**

* *Pseudomonas aeruginosa* and *Pseudomas putida.*

† *Staphylococcus aureus, Staphylococcus epidermidis,* and *Staphylococcus haemolyticus; Streptococcus salivarius.*

‡ *Escherichia coli, Proteus mirabilis, Morganella morganii, Providencia stuartii, Enterobacter cloacae,* and *Klebsiella ozaenae.*

Table 4.—Clinical Results

	No. (%)		
Group	Cure	Improvement	Failure
A	8 (40)	5 (25)	7 (35)
B	17 (85)	3 (15)	. . .
C	15 (75)	4 (20)	1 (5)

Table 5.—Bacteriological Results

	No.(%)		
Group	Eradication	Persistence	Superinfection
A	8 (40)	8 (40)	4 (20)
B	19 (95)	1 (5)	. . .
C	17 (85)	1 (5)	2 (10)

Table 6.—Responsible Bacteria Isolated 24 Hours After the End of Therapy*

Group		
A	B	C
Pseudomonas (7)	. . .	*Pseudomonas* (1)
Staphylococcus aureus (3)	. . .	*S aureus* (3)
Morganella morganii (1)	. . .	. . .
Streptococcus (1)	. . .	. . .
. . .	*Escherchia coli* (1)	. . .

* The numbers in parentheses indicate the number of bacteria.

Bacterial cultures of middle ear effusion were performed 24 hours after the interruption of the therapy, and no ciprofloxacin resistance was detected. All patients who were clinically and bacteriologically cured 24 hours after the interruption of the treatment confirmed their clinical status 14 days after the end of the therapy (follow-up). No side effect was recorded in any patient, and no worsening of the audiometric function related to the local therapy (groups B and C) was observed.

The bacteriological and clinical cure rates observed in groups B and C were statistically higher than those in group A ($P<.05$).

COMMENT

The infectious processes of the middle ear are usually difficult to cure, probably because of the low concentrations of antibiotics at this site and because of the frequent etiologic role of *Pseudomonas*, which is resistant to several classes of antibiotics. Also, in the present study the frequency of detection of *Pseudomonas* was high (47% of the total number of isolated bacteria).

On the other hand, in general medical practice, patients affected by suppurative COM seldom undergo microbiological examination of the ear effusion and are frequently unsuccessfully treated with conventional antibiotic therapy that does not include *Pseudomonas* in its antibacterial spectrum of activity. Sometimes, antibacterial agents such as neomycin are utilized for topical treatment, but their use is controversial because of the ototoxicity that can result, especially in case of tympanic membrane perforation. In our study, prior conventional treatments with parenteral, oral, or topical drugs had already failed in 38 of the 60 patients under examination.

Few data concerning the treatment of bacterial otitis with oral ciprofloxacin are available in the literature at present, and our results are not in agreement with them. In 1985 Fujimaki et al[8] and Mori et al[9] in two different studies performed in Japan reported a high frequency of clinical resolution and bacteriological eradication following the oral administration of 200 mg of ciprofloxacin three times a day. Good results were also reported by Van de Heyning et al[10] in 28 patients affected by suppurative COM, but at much higher dosages (750 mg twice a day).

Our opinion, based on the results of our study, is that low dosages of ciprofloxacin are not sufficient to effectively cure bacterial otitis and that higher dosages are probably advisable. However, we recorded extremely favorable results following topical treatment of ciprofloxacin both alone and in association with oral administration of the same drug. The local treatment was very effective, and we frequently observed eradication of the responsible bacteria and disappearance of the middle ear effusion soon after three to four instillations of drops. The contemporary administration of ciprofloxacin did not increase the percentage of cure observed with topical therapy, but its use in combination could probably be recommended for severe COM, especially when complications are possible.

Ciprofloxacin locally administered is very effective in curing COM in the acute stage. The patients' compliance in this treatment; the high antibacterial activity against *Pseudomonas*, which is frequently responsible for these infections; and the complete absence of ototoxicity of the drug could make the use of such a formulation a first-choice therapy for the treatment of COM in the acute stage. Finally, the absence of side effects on the growth cartilage of children, which is possible with systemic use of ciprofloxacin, makes its topical use possible in pediatric patients as well.

The ciprofloxacin tablets and powder used in this study were kindly provided by Bayer Italia Spa, Milan, Italy.

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Cytokeratins in Induced Epidermoid Formations and Cholesteatoma Lesions

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• The expression of cytokeratins varies with the type of epithelium, the state of differentiation, and pathological conditions. In this study, the differential expression of cytokeratins in external meatal skin and middle ear epithelium was used for a pathogenetic study of cholesteatoma lesions and infection-induced epidermoid formations in the middle ear of the rat. Immunocytochemistry generally revealed an epidermal-type cytokeratin profile in the cholesteatoma matrix, except for the focal expression of nonepidermal cytokeratins at the invasion front. Comparable observations were made in the middle ear of the rat after an infection-induced invasion of epidermal cells from the meatal skin. An infection-induced–cornifying metaplastic lesion of the middle ear epithelium revealed nonepidermal cytokeratin expression. The results of this combined study suggested that the cholesteatoma specimens studied had an epidermal origin. The expression of nonepidermal cytokeratins was considered to result from a state of hyperproliferation rather than from metaplasia.

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Cholesteatoma can be defined as the presence of a cornifying squamous epithelium in the middle ear cavity. It can be associated with the destruction of bone. The cause of cholesteatoma is still a matter of debate, because clinical and histopathological observations have not always produced conclusive evidence of the site of origin, but it is generally accepted that individual cases of cholesteatoma can have different causes. Epidermal cells from the external meatus (including the tympanic membrane) can invade the middle ear through preexisting perforations,[1] retraction pockets,[2] or inward proliferation of basal epidermal cells[3]; or the cause can be iatrogenic as a consequence of tympanoplasty.[4] Alternatively, squamous metaplasia of the middle ear epithelium and congenital epidermoid rests in the middle ear have also been proposed as possible sources of cholesteatoma.[4,5]

To our knowledge, the mechanism that triggers this behavior of epithelial cells has not yet been elucidated, but inflammation and eustachian tube obstruction are assumed to be the most likely candidates.

A new approach that can be helpful in the study of cholesteatoma development is the identification of their intermediate-filament proteins. Intermediate-filament proteins are important constituents of the intracellular cytoskeleton with a typical tissue-specific distribution pattern. In epithelial cells, the intermediate filaments (tonofilaments) are composed of cytokeratins.[6,7]

In humans, 19 different cytokeratin types can be divided into two major groups of basic and acidic proteins that combine in pairs. In one individual cell type, 2 to 10 individual cytokeratins can occur. Their expression has been shown to depend on the type of epithelium, the stage of differentiation, the functional state, and environmental conditions.[6,7] According to these properties, cytokeratin expression can contribute to a better understanding of the origin of cholesteatoma,[8-10] while possible changes in the cytokeratin

Table 1.—Cytokeratin Antibodies Applied in This Study

Source, y	Antibody	Specificity for Cytokeratin No.	Dilution
Ramaekers et al,[12] 1983	pKer	Several	1:40
Ramaekers et al,[13] 1987	RCK 102	5 + 8	Undiluted
	RCK 103	Several	1:2
	RCK 105	7	1:3
	RKSE 60	10	1:2
Broers et al,[14] 1986	CK 18-2	18	Undiluted
Lane et al,[15] 1985	LP2K	19	Undiluted
van Muijen et al,[16] 1986	1C7	13	Undiluted
	6B10	4	Undiluted
Schaafsma et al,[17] 1989	M20	8	1:5

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profile of meatal skin invading into the middle ear cleft can be established.

In this study, we examined the cytokeratin expression patterns of experimentally induced epidermoid formations in the middle ear of the rat. The results obtained from this experimental study were related to the cytokeratin profiles observed in human cholesteatoma, external meatal skin, and middle ear mucosa.

MATERIALS AND METHODS

For the induction of purulent otitis media, 20 adult Wistar rats (body weight, about 170 g) from a *Mycoplasma pneumoniae*-contaminated strain that displayed clinical symptoms like sneezing and rhinorrhea were used. The animals were checked otoscopically for the absence of otitis, and eustachian tube obstruction was performed according to the method described by Kuijpers and van der Beek[11] by electrocautery with the rats under fentanyl citrate (Hypnorm) (intramuscularly, 0.05 mL/100 g of body weight) and diazepam (intraperitoneally, 0.05 mL/100 g of body weight) anesthesia. The condition of the middle ear was checked by otoscopy on days 1, 2, 4, and 8 after the operation and subsequently at weekly intervals.

After survival times varying from 1 week up to 6 months, the animals were killed by an intracardiac injection of pentobarbital sodium (Nembutal) and decapitated. The middle ear and part of the external meatal skin were dissected and processed for paraffin embedding after fixation in 4% formaldehyde solution in 0.1-mol/L phosphate buffer (pH, 7.4) at 4°C for 2 days; this was followed by decalcification in edetic acid (EDTA) (10%; pH, 7.4) for 2 weeks or immediate storage in a decalcification solution (10% edetic acid and 7.5% polyvinylpyrrolidone in 0.1-mol/L TRIS-hydrochloric acid buffer; pH, 7.4) at 4°C for 2 weeks. After rinsing in the same solution without edetic acid for 2 hours, these samples were frozen in liquid nitrogen and cryosectioned at 7 μm. Sections were collected on poly-L-lysine-coated slides, air dried, and stored at −70°C until use.

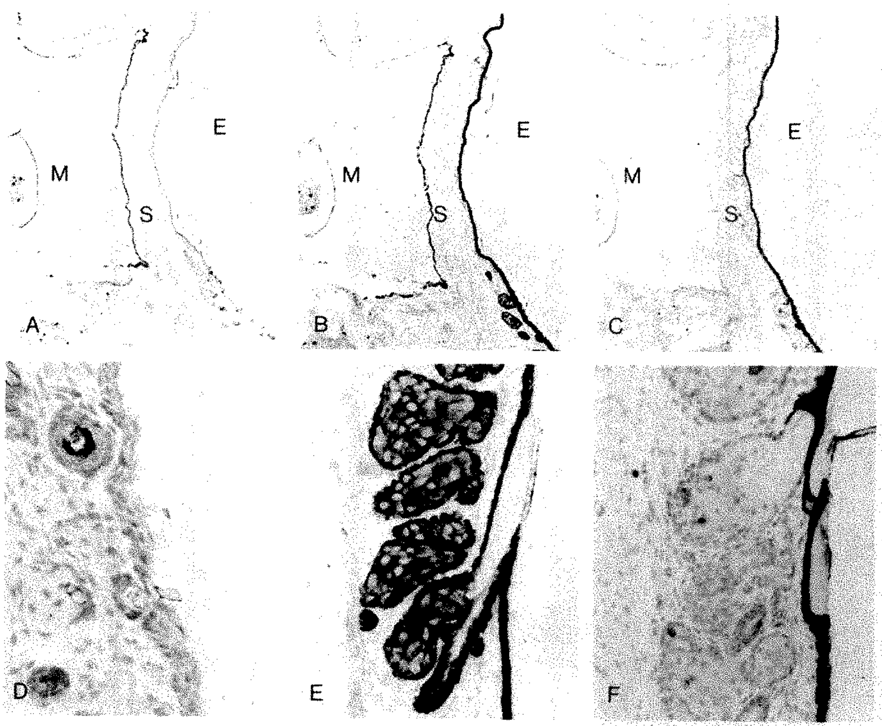

Fig 1.—Immunohistochemical staining of rat meatal skin and middle ear epithelium with the monoclonal antibodies RCK 102 (A and D), RCK 103 (B and E), and RKSE 60 (C and F). RCK 102 only reacts with the middle ear epithelium and the inner root sheath of the hair follicles. With RCK 103, both external meatal skin, including hair follicles and sebaceous glands, and middle ear epithelium are stained. Staining with RKSE 60 is limited to the suprabasal layers of the epidermis. E indicates external meatus; M, middle ear; and S, Shrapnell's membrane (original magnification, top panels ×35; bottom panels ×100).

Table 2.—Cytokeratin Expression in External Meatus and Middle Ear of Rats and Humans*

		Rats			Humans		
Antibody	CK	Middle Ear Epithelium	Meatal Skin	Invaded Skin	Middle Ear Epithelium	Meatal Skin	Cholesteatoma Matrix
RCK 102	5 + 8	+	−†	−	+	+	+
RCK 103	. . .	+	+	+	+	+	+
RCK 105	7	+/−	−	−	+	−	−
RKSE 60	10	−	+‡	+§	−	+‡	+‖
CK 18-2	18	+	−	−	+	−	−
LP2K	19	+	−	−	+	−	−¶
6B10	4	+/−	−	−¶	+/−	−	−¶
1C7	13	−	−	−¶	+/−	−	−¶
M 20	8	−	−	−	+	−	−
pKer	. . .	+	+	+	+	+	+

*CK indicates cytokeratin; +, homogeneous positive reaction; +/−, heterogeneous positive reaction; and −, negative reaction.

†Only inner root sheath of hair follicles.

‡Suprabasal staining.

§Suprabasal staining but absent at the migrating front.

‖Suprabasal staining, but focally disturbed and absent at the migrating front.

¶Focally positive and at the migrating front.

For immunocytochemistry, the sections were fixed in acetone (at 4°C for 10 minutes), rinsed in phosphate-buffered saline solution (PBSS), and incubated with different monoclonal antibodies with known specificities for human cytokeratin,[5] either as an undiluted culture supernatant or diluted in PBSS for 45 minutes (for specifications and references, see Table 1). The sections were washed in PBSS and incubated with horseradish peroxidase-conjugated rabbit anti-mouse (or swine anti-rabbit for the polyclonal serum pKer) immunoglobulin that contained 5% (vol/vol) rat serum for 30 minutes. After washing in PBSS and sodium acetate buffer (pH, 4.9) for 5 minutes, peroxidase activity was detected by using a mixture composed of 0.02% 3-amino-9-ethylcarbazole, 5% dimethylformamide, and 0.01% hydrogen peroxide in sodium acetate buffer (pH, 4.9). The sections were counterstained with Mayer's hemalum and mounted in glycerin jelly. As a control, the primary antibody was omitted. Compar-

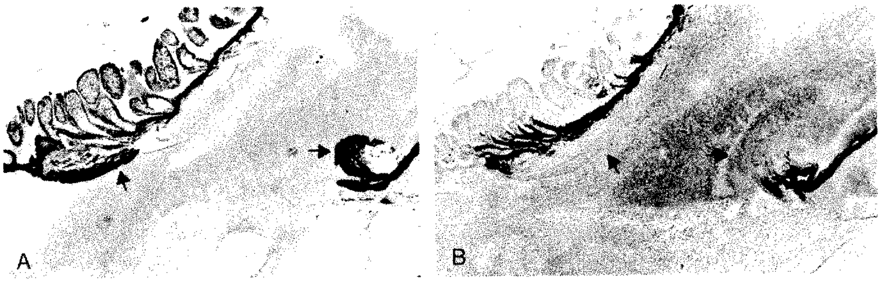

Fig 2.—Immunohistochemical staining of rat healing tympanic membrane perforation with the monoclonal antibodies RCK 103 (A) and RKSE 60 (B). Note the selective absence of RKSE 60 staining at the edges of the healing membrane (arrows) (original magnification ×35).

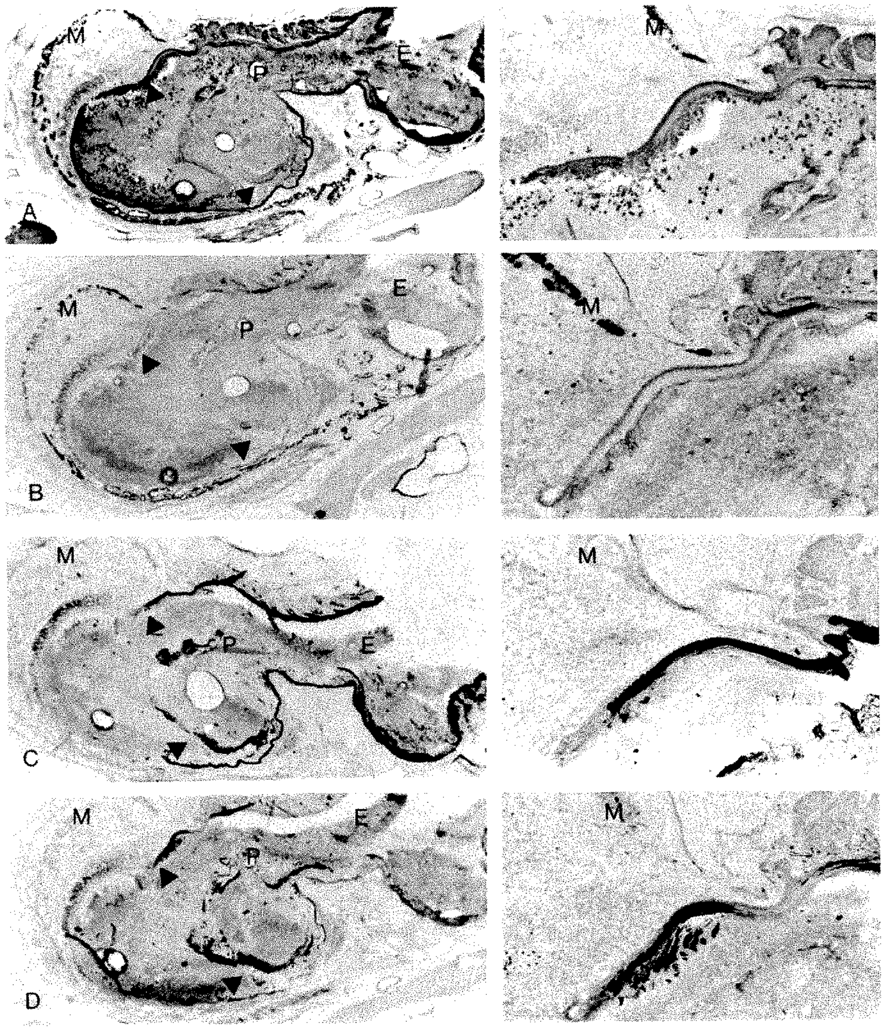

Fig 3.—Immunohistochemical staining shows the cytokeratin profile of infection-induced invasion of meatal epidermis into the rat middle ear cavity with the monoclonal antibodies RCK 103 (A), RCK 102 (B), RKSE 60 (C), and 1C7 (D). The left panels show surveys, and the right panels show higher magnifications of the invading epithelium (arrowheads in left panels). Note the differential staining of the skin of the external meatus (E) and middle ear epithelium (M), the focal staining with 1C7, and the absence of staining at the invading front with RKSE 60. P indicates tympanic membrane perforation (original magnification, left panels ×10; right panels ×35).

ison of the specimens stored in edetic acid with freshly dissected specimens showed that the decalcification solution did not have any effect on the cytokeratin expression patterns detected with the antibodies tested.

In some cases, paraffin sections were used for immunocytochemistry. Before incubation with the primary antibodies, these sections were treated with 0.1% pronase in PBSS at 37°C for 10 minutes.

In addition to these animal tissues, the cytokeratin profiles of 10 cases of human cholesteatoma obtained from different clinical cases and four biopsy specimens of normal human meatal skin and middle ear epithelium were studied by using the same panel of antibodies.

RESULTS

Normal Rat Ear

In the normal rat, a positive staining of the external meatal skin, including the sebaceous glands, hair follicles, and the outer layer of the tympanic membrane, was found with the antibodies pKer and RCK 103. With RKSE 60, only the suprabasal cells were positive, while staining with RCK 102 was limited to the inner layer of the root sheath of the hair follicles (Fig 1). All other antibodies tested were negative.

The middle ear epithelium showed a homogeneous staining with the antibodies pKer, RCK 102, RCK 103, LP2K, and CK 18-2, both in the flat squamous epithelium and in the mucociliary tracts. With RCK 105 and 6B10, the squamous epithelium revealed a scattered positive reaction. With RCK 105, only a subpopulation of the cells in the mucociliary tracts was stained, while no reaction was found with 6B10. The antibodies RKSE 60 and 1C7 failed to show any reaction in the middle ear epithelium. With the antibody M 20, no reaction at all was established in rat epithelia. The data obtained are summarized in Table 2.

Eustachian Tube Obstruction

In all ears with obstructed eustachian tubes, an accumulation of purulent fluid was observed otoscopically within 2 days after the operation, followed by a spontaneous perforation of the tympanic membrane and otorrhea between 2 and 8 days. In the majority of the ears, spontaneous closure of the perforation was seen during the second week. In six ears, otorrhea persisted for longer periods, and in two of

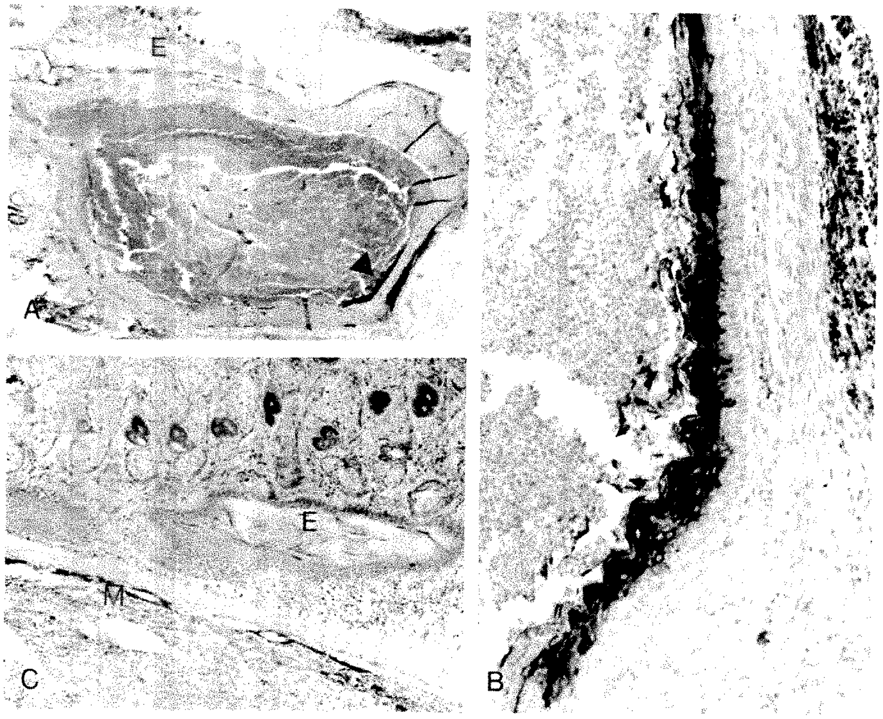

Fig 4.—Immunohistochemical staining of infected rat middle ear with metaplastic area of cornifying epithelium (arrowhead) with RCK 102. A, Survey. B, Higher magnification of metaplastic epithelium shows suprabasal staining. C, Higher magnification of meatal skin area (E). Staining is limited to inner root sheath of hair follicles and middle ear epithelium (M) (original magnification, A ×20; B and C ×100).

these rats, killed after 4 and 11 weeks, respectively, sections displayed the invasion of epidermal cells from the meatal skin into the middle ear cavity. The epithelium migrated on top of the infection-induced fibrous tissue. The latter contained the original middle ear epithelium, visible as cystlike structures.

Immunocytochemistry demonstrated that the cytokeratin expression in the invading epithelium was identical to that in the native meatal skin, except for the frontal area, where staining with RKSE 60 was absent. Remarkably, in this area, the antibodies 1C7 and 6B10, which are not expressed in the meatal skin, showed a distinct reaction with the suprabasal epithelial cells (Fig 2). A comparable phenomenon was seen at the edges of tympanic membrane perforations in the ears in which the membrane had started to heal. This is illustrated for RCK 103 and RKSE 60 in Fig 3.

No fundamental difference was seen between the cytokeratin profile in the residual middle ear epithelium and the normal ear, except for the occasional absence of cytokeratin 7 expression, as revealed by RCK 105.

In the ears in which the tympanic perforations were found to be healed, the middle ear cavity revealed a varying amount of fibrous tissue that enclosed the original middle ear epithelium and a central core of pus. On top of this tissue, signs of the formation of a new epithelial layer could be observed locally. In three animals that survived for 4 months after eustachian tube obstruction, isolated areas of stratified squamous epithelium were found. In two ears, this epithelium consisted of noncornifying epithelium, and in the third ear, it clearly demonstrated cornification with a desquamating stratum corneum, a stratum granulosum that contained keratohyaline granules, and a stratum lucidum. Incubation of sections from this ear with the polyclonal antibody pKer showed a homogeneous staining of this epithelium and the meatal skin. The antibody RCK 102 displayed a marked positive reaction in the suprabasal layers of the stratified epithelium (Fig 4). In the external meatal skin, only the inner layer of the root sheath of the hair follicles stained positive. Because it concerned paraffin-embedded specimens, no other cytokeratin antibodies could be tested, because their epitopes were destroyed by this procedure.

A specimen embedded in paraffin, obtained from an animal that survived for 4 weeks, displayed a total perforation of the tympanic membrane and a dry middle ear cavity that was completely lined with squamous epithelium, continuous with the meatal skin. In this case, testing with the antibody RCK 102 failed to show any reaction with the invaded epithelium.

Human Specimens

The cytokeratin profiles observed in specimens from normal human meatal skin and middle ear epithelium are summarized in Table 2. They revealed a comparable differential expression to that observed in the same tissues of the rat. The simple epithelium of the middle ear stained homogeneously with the whole panel of antibodies tested, with the exception of RKSE 60, while only scattered cells stained with 6B10 and 1C7. In contrast to the rat middle ear, the antibody M 20 showed a homogeneous positive reaction. The epithelium of the meatal skin showed a positive reaction with the polyclonal antibody pKer and the monoclonal antibodies RCK 102 and RCK 103, including hair follicles and sebaceous glands. The antibody RKSE 60 only stained the suprabasal epithelial cells (Fig 5).

The histological appearance of the cholesteatoma specimens was largely divergent with respect to the thickness of the epithelium, the infiltration of epithelial cells into the perimatrix, and the presence and number of inflammatory cells in the perimatrix. The cytokeratin profile, displayed by all 10 cholesteatoma specimens studied, was generally similar to that observed in the meatal skin, except for the advancing front at the junction with the middle ear epithelium. At the margin of this area, staining with RKSE 60 was almost completely absent or had shifted toward more superficial cell layers (Fig 6). With the antibodies 1C7, 6B10, and LP2K, which normally do not react with cornifying

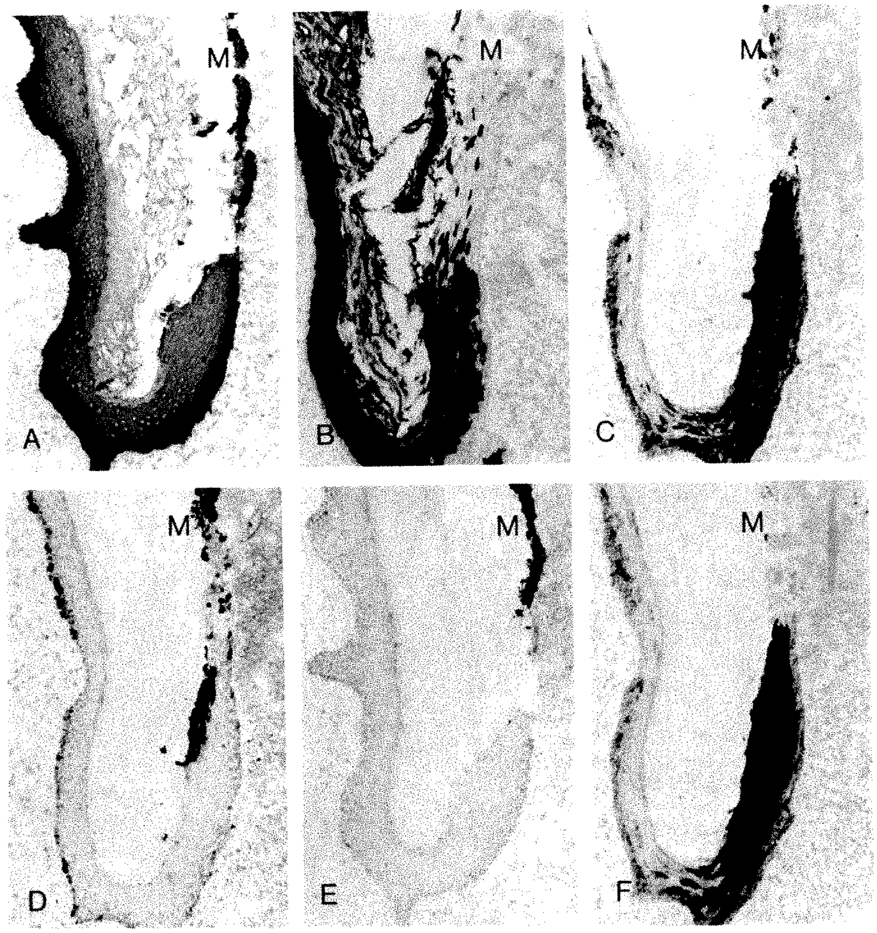

Fig 5.—Immunohistochemical staining of junctional area of cholesteatoma matrix and middle ear epithelium (M). A, RCK 103. B, RKSE 60. C, 1C7. D, LP2K. E, M20. F, 6B10. Note the expression of nonepidermal cytokeratins and the absence of cytokeratin 10 expression (RKSE 60) at the front of the invading epithelium (original magnification ×40).

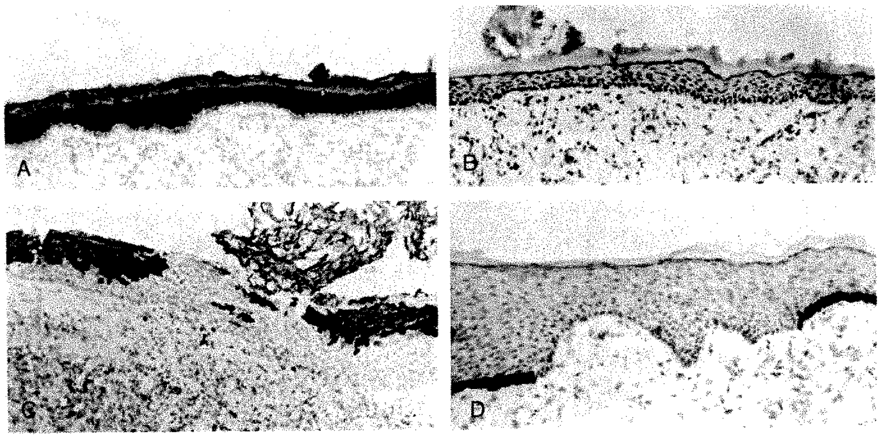

Fig 6.—Immunohistochemical staining of normal human meatal skin epithelium (A and B) and cholesteatoma matrix (C and D). Note the aberrant reaction of RKSE 60 (A and C) and LP2K in the cholesteatoma matrix (B and D) (original magnification ×40).

epithelium, a positive reaction was found in this area. This reaction was strongest at the margin of the advancing front and diminished toward more distant areas (Fig 6). In these specimens, a comparable focal disturbance of the cytokeratin expression was found far distant from this invading front (Fig 5).

COMMENT

The results presented in this study demonstrate a distinct divergence of cytokeratin expression patterns between external meatal skin and middle ear epithelium, both in humans and in rats. This is in line with the general rules for cytokeratin expression in simple and complex epithelia[7] and with the cytokeratin profiles established in skin[6,15] and respiratory epithelia.[18] Comparison of these cytokeratin-staining patterns, displayed by meatal skin and middle ear epithelium in humans and in rats, demonstrates a close similarity in reaction patterns between these species, with only minor differences for antibodies M 20 and RCK 102. Apparently M 20 does not react with a cytokeratin epitope in the rat. This assumption is further supported by the observation that the epithelia in the nasopharynx were also negative. Although antibody RCK 102 does react with rat cytokeratin epitopes, its staining reaction in the meatal skin is virtually limited to the inner layer of the root sheath of the hair follicles.

The similarity between the cytokeratin patterns of the cholesteatoma matrix and the meatal skin corresponds with the findings made by van Blitterswijk and Grote[10] and Broekaert et al[9] and provides strong evidence that these cholesteatoma lesions had an epidermal origin. However, the focal expression of cytokeratins 4 (6B10), 13 (1C7), and 19 (LP2K), together with a disturbed cytokeratin 10 (RKSE 60) expression in the cholesteatoma matrix, is at variance with this assumption and needs further explanation. These are nonepidermal cytokeratins. Cytokeratin 19 is preferentially found in simple epithelia and in the basal compartment of some noncornifying stratified epithelia,[19] while cytokeratins 4 and 13 are mainly restricted to noncornifying squamous epithelium. Based on the focal expression of nonepidermal cytokeratins in the cholesteatoma matrix, together with the cornification of cultured middle ear epithelium observed in vitro, van Blitterswijk and Grote[10] did not exclude a metaplastic origin of cholesteatoma. On the other hand, Broekaert et al[9] considered this focal expression of nonepidermal cytokeratins to be a hyperproliferative state as encountered in other hyperproliferative epidermic diseases.[20] The present experimental study on the rat can probably contribute to a better understanding of the origin and behavior of ectopic cornifying epithelium in the middle ear cavity.

The study shows that purulent otitis media associated with a tympanic membrane perforation can lead to the invasion of meatal skin into the middle ear cavity. This corresponds with comparable studies on guinea pigs.[21]

These observations favor the assumption that infection can be considered to be an important trigger in the ectopic expansion of cornifying epithelium into the middle ear cavity. The invading epithelium from the meatus generally retains its original cytokeratin profile. Strikingly, however, at the invading front, a local expression of nonepidermal cytokeratins (Nos. 4 and 13) was noticed, while cytokeratin 10 (RKSE 60) expression, which is a reliable marker of cornification, was absent. A comparable phenomenon was observed at the perforation edges of the healing tympanic membrane, at the advancing front of the cholesteatoma matrix, and also focally distant from this area. This points to locally altered terminal differentiation. Therefore, the focal expression of nonepidermal cytokeratins in cholesteatoma lesions and the aberrant behavior of cytokeratin 10 expression can be explained by assuming that these findings were caused by local differences in the state of differentiation, correlated with hyperproliferation, rather than by a metaplastic origin. In this context, ears with cholesteatoma have often been treated before surgery for a long period with ear drops that contain corticosteroids. Therefore, a drug-induced change in the condition of the epithelium, including the cytokeratin profile, cannot be excluded. Eichner et al[22] showed such changes in cytokeratin expression patterns with hydrocortisone in tissue culture.

Apart from an epidermal genesis, the presence of an isolated area of cornifying epithelium, in one of the rats studied, favors metaplasia of the middle ear epithelium as an alternative source of cornifying epithelium in the middle ear as was suggested by Sadé et al.[4] Especially the staining of this area with the antibody RCK 102, which also stains the middle ear epithelium but not the meatal skin, provided conclusive evidence for a metaplastic origin in one animal. Such a genesis of cholesteatoma, suggested to account for about 4% of the total number encountered,[4] is difficult to prove clinically, because these lesions will usually remain unnoticed until the tympanic membrane perforates and infection occurs. This makes them indistinguishable from a cholesteatoma that originates from an ingrowing epidermis. The present study demonstrates that the cytokeratin expression seems to be very useful to differentiate between these types of cholesteatoma.

Summarizing, this immunohistochemical study demonstrates that on account of the similarity among the cytokeratin profiles of meatal skin, invading epithelium, and cholesteatoma, it can be concluded that the cholesteatoma specimens studied had an epidermal origin. The focal presence of nonepidermal cytokeratins in the cholesteatoma matrix may refer to hyperproliferative activity rather than to a metaplastic origin. In addition, the results of this experimental study on the rat support the assumption that cornifying epithelium can arise from the middle ear epithelium by an infection-induced metaplasia.

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Observations of the Anterior Epitympanic Recess in the Human Temporal Bone

Tatsuya Yamasoba, MD; Takehiko Harada, MD; Yasuya Nomura, MD

• The structure of the anterior epitympanic recess was examined in 50 human temporal bones. The recess was found in 48 temporal bones (96%) and showed three different structural types. In type A, the least developed type (38%), a main cavity is seen above the tensor tympanic fold. The recess is divided into two cavities by the tensor tympanic fold, which stretches to the anterosuperior tympanic tegmen in type B, the intermediate type (40%). The tensor tympanic fold is fused with the superior mallear fold in type C, the best-developed type (18%), with the recess being contiguous with the eustachian tube. The shape of the anterior epitympanic recess is influenced by the ratio between the cavities above and below the tensor tympanic fold, ie, by the embryologic development of the saccus anticus and the anterior saccule of the saccus medius. The structural variations in this recess must be kept in mind during the surgical management of middle ear diseases.

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The anterior epitympanic recess is a separate cavity of varying form and size, situated anterior to the cog. Wigand and Trillsch[1] first described this cavity as the "sinus epitympani," and various terms have been used since then: anterior epitympanic recess,[2] anterior epitympanic cell,[3] anterior epitympanic space,[4] supratubal recess,[5] and supratubal space.[6] Its boundaries include the middle cranial fossa superiorly, the petrous apex and middle cranial fossa anteriorly, the cog posteriorly, the tympanic bone laterally, and the facial nerve and geniculate ganglion medially. Its inferior border has been regarded as either the tensor tympanic semicanal[1] or the tensor tympanic fold.[4,5] During the surgical management of middle ear diseases, it is necessary to keep in mind such structural variations of the anterior epitympanic recess and the position of its adjacent tissues.

As Proctor[7] pointed out, the middle ear spaces are formed by four endothelial sacs extending from the eustachian tube. The tensor tympanic fold is formed where the saccus anticus meets the anterior saccule of the saccus medius. The cog may represent the separation between the anterior saccule of the saccus medius and the remaining saccus medius.[5]

The purpose of this study is to classify the shape of the anterior epitympanic recess and to clarify the correlation between its shape and its embryologic origin.

MATERIALS AND METHODS

Fifty well-pneumatized human temporal bones, 26 right and 24 left from 30 individuals, were examined. The temporal bones were decalcified with 10% hydrochloric acid after fixation with 10% formaldehyde solution. The bones were cut parallel to the tympanic membrane, and the cut surfaces of the middle ears were examined under an operating microscope.

The shape of the anterior epitympanic recess was classified according to the degree of its development. In addition, we measured the following distances: (1) the distance from the tensor tympanic tendon to the deepest point of the anterior epitympanic recess (distance a); (2) the length of the tensor tympanic fold (distance b); and (3) the distance from the top of the cavity below the tensor tympanic fold to the inferior border of the tensor tympanic semicanal (distance c). A schematic drawing of these measurements is presented in Fig 1.

RESULTS

The anterior epitympanic recess was identified in 48 of the 50 temporal bones (96%). In two specimens, the anterior epitympanic recess did not develop, and the bone anterior to the malleus head was pneumatized with many small cells (Fig 2). In all cases in which the anterior epitympanic recess developed, the cog was found in front of the malleus head projecting downward from the tympanic tegmen. The average distance from the tympanic

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tegmen to the tip of this plate was 2.0 ± 0.8 mm.

The anterior epitympanic recess was classified into three structural types (Fig 3):

1. In type A (Fig 4, top), the tensor tympanic fold stretches along the superior border of the tensor tympanic semicanal and is commonly attached to a thick, bony plate anteriorly. The cavity above the tensor tympanic fold appears as a bulge distinct from the eustachian tube. The cavity below this fold is a small depression from the eustachian tube. We included in this type cases in which the distance between the inferior border of the tensor tympanic semicanal and the deepest point of the depression (distance c) was less than 2 mm. Nineteen (38%) of the 50 recesses examined were type A.

2. In type B (Fig 4, center), the tensor tympanic fold extends from the tensor tympanic tendon to the anterosuperior tympanic tegmen. The anterior epitympanic recess is divided into two cavities by the tensor tympanic fold, and both cavities are well developed. The cavity below the tensor tympanic fold is generally contiguous with the eustachian tube. The tensor tympanic fold is usually attached to a thin, bony plate anterosuperiorly. Twenty recesses (40%) were included in this type.

3. In type C (Fig 4, bottom), the tensor tympanic fold is fused with the superior mallear fold and stretches from the cog to the neck region of the malleus and to the tensor tympanic tendon. The cavity anterior to these

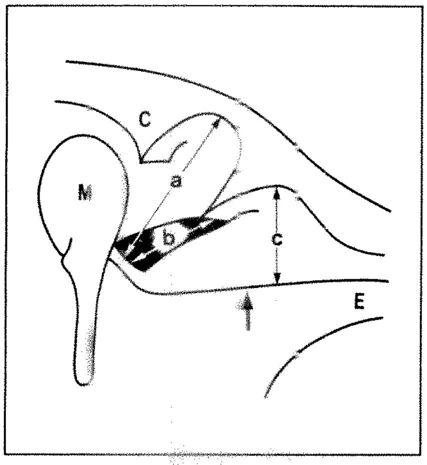


Fig 1.—Lateral view of anterior epitympanic recess of right temporal bone. Measurements of the following three distances were made: distance a, from the tensor tympanic tendon to the deepest point of the anterior epitympanic recess; distance b, tensor tympanic fold length; and distance c, from the inferior border of the tensor tympanic semicanal to the deepest point of the cavity below the tensor tympanic fold. C indicates cog; E, eustachian tube; and M, malleus head.

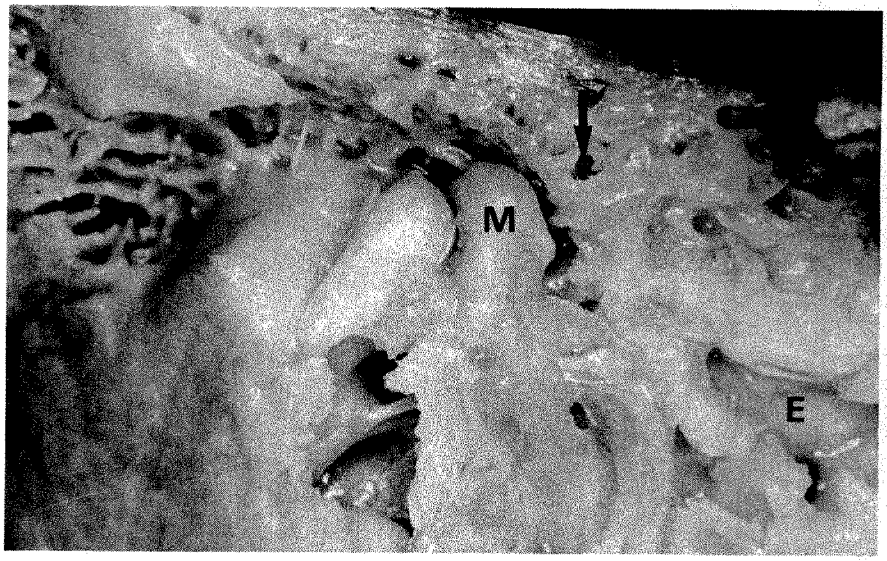
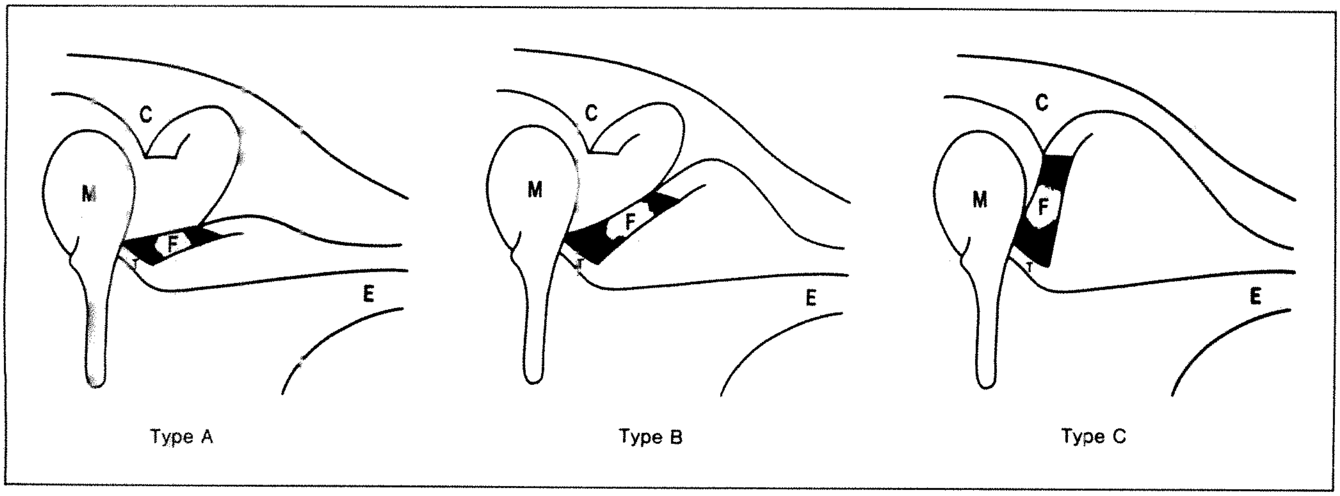


Fig 2.—Lateral view of the right temporal bone. No anterior epitympanic recess is visible, with cellular bone (arrow) anterior to the malleus head. E indicates eustachian tube; M, malleus head.

Fig 3.—Schematic drawings of the anterior epitympanic recess for types A, B, and C. All views are of the right ear from the lateral side. C indicates cog; E, eustachian tube; F, tensor tympanic fold; M, malleus head; and T, tensor tympanic tendon.



folds continues to the protympanum and eustachian tube. Nine recesses (18%) were found to be type C.

The results of measurement of distances a through c are shown in the Table. Because distances a and c increased in the order of types A, B, and C, the anterior epitympanic recess in type C was considered the best developed and in type A the least developed. The length of the tensor tympanic fold (distance b) was the longest in type C and the shortest in type A.

In addition to these results, there was a tendency for the development of the cells around the anterior epitympanic recess to be related to recess size. Type C had well-pneumatized cells around the anterior epitympanic recess, while in type A, the bones around the anterior epitympanic recess were relatively acellular. No correlation was found between the degree of pneumatization of the whole temporal bone and the size of the anterior epitympanic recess. Furthermore, no direct communication between the anterior epitympanic recess and its surrounding cells was found in any case.

COMMENT

As Proctor[7] pointed out, the middle ear spaces are formed by four endothelial sacs, or pouches, extending from the eustachian tube between the third and seventh fetal months. Where these pouches come into contact, mucosal folds are formed. The anterior

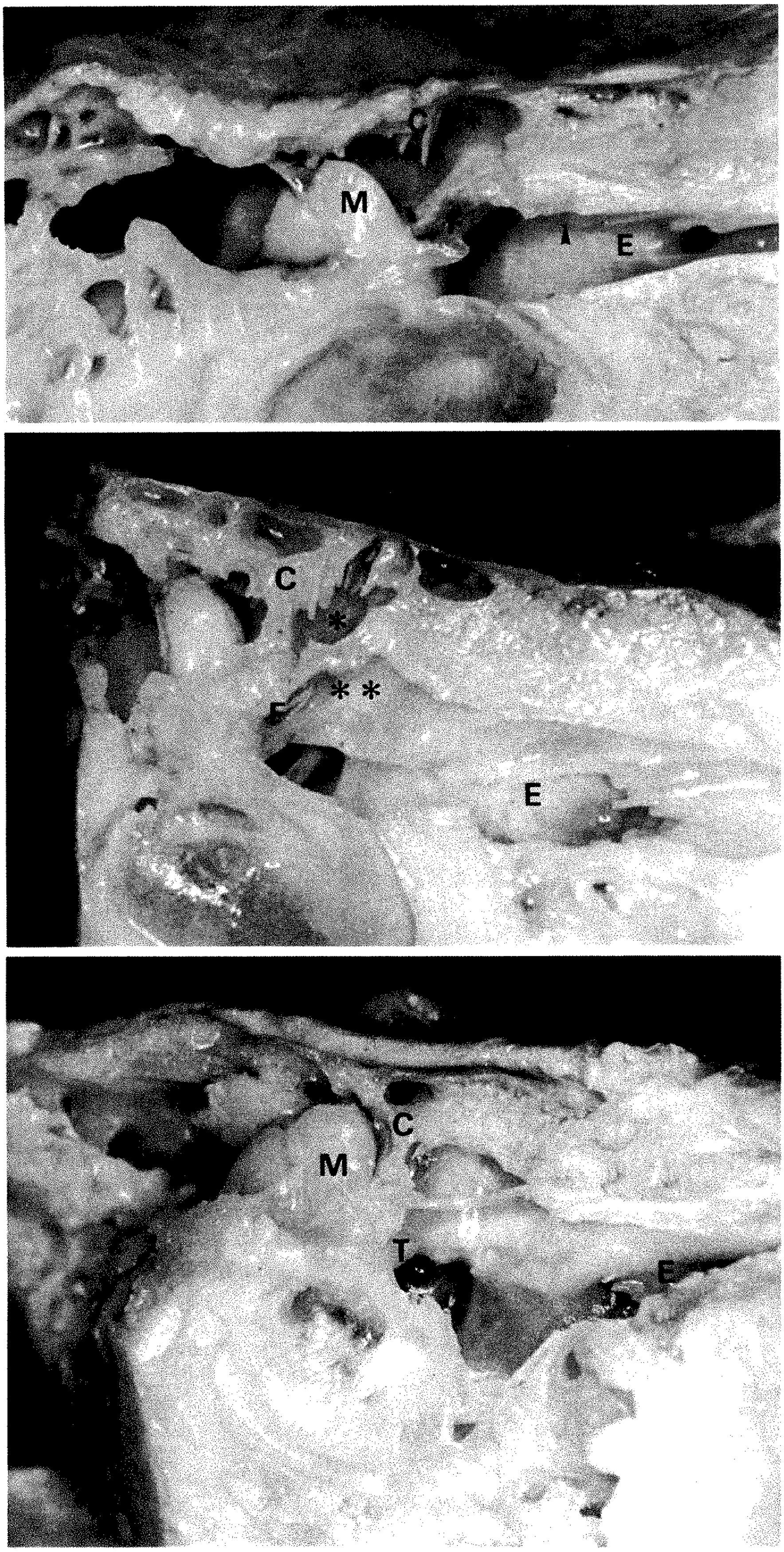


Fig 4.—Anterior epitympanic recess of types A, B, and C. All views are of the right ear from the lateral side. Top, Structural type A. A definite bulge (asterisk) is seen entirely enclosed by the surrounding bony structure except for a narrow opening below the cog (C). A thick bony plate close to the tensor tympanic tendon is visible, with a short tensor tympanic fold (F) between them. A poorly developed recess is seen (arrowhead). E indicates eustachian tube; M, malleus head. Center, Structural type B. The recess is separated into two compartments. The upper cavity (asterisk) is bordered inferiorly by the tensor tympanic fold (F) and posteriorly by the cog (C). The lower cavity below the tensor tympanic fold (two asterisks) is contiguous with the eustachian tube (E). Bottom, Structural type C. No well-defined anterior or inferior boundaries are visible, with the recess sloping down to the eustachian tube (E). A tensor tympanic mucosal fold from the cog (C) to the tensor tympanic tendon (T) and neck region of the malleus (M) can be seen. Anterior to this fold, no folds are visible.

epitympanum may be formed by both the saccus anticus and the saccus medius.

The saccus medius extends upward through the isthmus tympani anticus, then breaks up into three saccules. The saccus anticus extends upward anterior to the tensor tympanic tendon and meets the anterior saccule of the saccus medius, thus forming the tensor tympanic fold. In types A and B in our classification, the tensor tympanic fold is commonly attached to a bony plate anteriorly. We regard this plate, as well as the tensor tympanic fold, as the marker of the site where the saccus anticus meets the anterior saccule of the saccus medius.

The cog is considered to separate the anterior saccule of the saccus medius from the remaining saccus medius, which forms the larger posterior epitympanum. Occasionally, the saccus anticus extends to the tegmen and as far posteriorly as the superior mallear fold. In this instance, the cog may be formed between the saccus anticus and the saccus medius.

Measurements of the Anterior Epitympanic Recess*

Distances, mm	Types A	Types B	Types C
a	3.3 ± 1.2	3.9 ± 0.8	4.2 ± 0.9
b	1.6 ± 0.9	2.6 ± 0.7	3.7 ± 0.6
c	1.2 ± 0.6	2.8 ± 0.5	4.7 ± 0.6

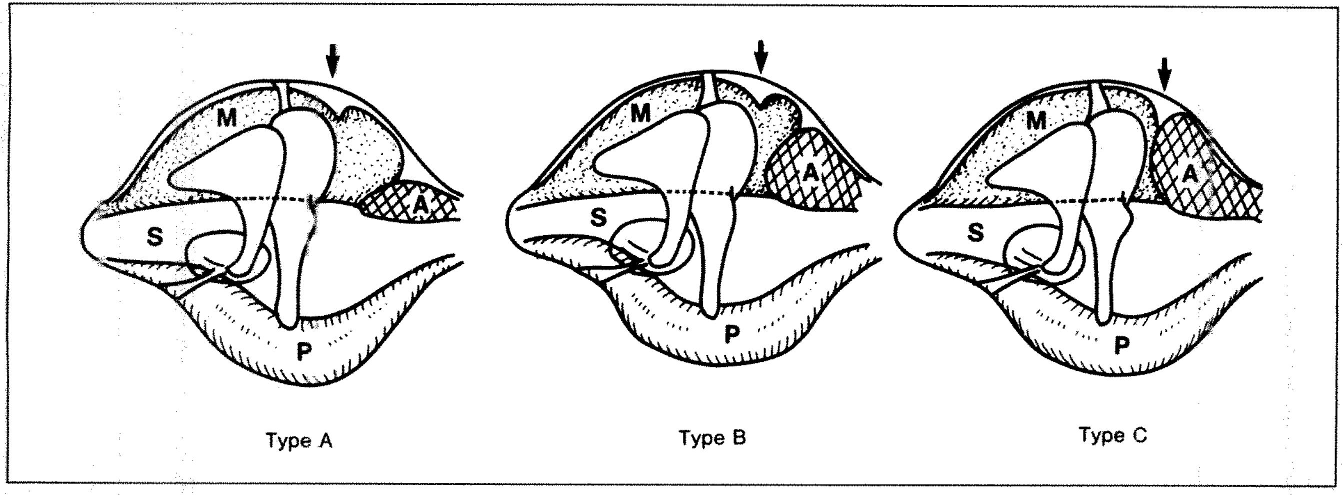
*See also Fig 1.

In our study, the anterior epitympanic recess was classified into three types. Hoshino[4] also found three structural types of this recess to which our classification bears some resemblance. The remarkable difference between his classification and ours is the site of the tensor tympanic fold in those cases in which no boundary membrane from this recess to the eustachian tube is found (type C in our classification). He recognized a poorly developed tensor tympanic fold making a thick, narrow shelf close to the cochleariform process in such an instance. However, we found the tensor tympanic fold from the cog to the neck region of the malleus and to the tensor tympanic tendon, fusing with the superior mallear fold. Furthermore, no mucosal fold was visible anterior to the cog.

Embryologically, in types A and B in our classification, the space above the tensor tympanic fold may be formed by the anterior saccule and the space below by the saccus anticus. In type C, the anterior epitympanic recess is considered to originate mainly from the saccus anticus. In other words, the variations of the shape of this recess are influenced by the ratio of development between the saccus anticus origin and the anterior saccule origin. When the saccus anticus develops as far posteriorly as the superior mallear fold, the shape of the anterior epitympanic recess represents type C. Type A is found when the saccus anticus is poorly developed. Type B is considered to be an intermediate form. The degree of development in these three types is in good agreement with the results of the measurement of distances a through c. A schematic drawing of the embryologic development of each type is shown in Fig 5.

Since Wigand and Trillsch[1] first described the anterior epitympanic space as a distinct structure and named it the *sinus epitympanum*, various names have been given to this cavity. Although the cog has been generally regarded as the posterior boundary of this cavity, its inferior boundary has not yet been confirmed. Wigand and Trillsch[1] regarded the tensor tympanic semicanal as its inferior border, but Hoshino[4] and Horn et al[5] considered the tensor tympanic fold as the floor of the anterior epitympanic recess. In our study, two cavities were recognized anterior to the cog, above and below the tensor tympanic fold. Because the embryologic origin of the cavity below the tensor tympanic fold in types A and B is considered to be the same as that of the cavity anterior to the cog in type C, the cavity below the tensor tympanic fold in types A and B should

Fig 5.—Origin and method of extension of tympanic pouches into the fetal tympanic cavity (modification of Proctor's drawings). In type A, there is a poorly developed saccus anticus with a well-developed anterior saccule; in type C, a well-developed saccus anticus as posteriorly as the supramallear fold; and type B is the intermediate form. A indicates saccus anticus; M, saccus medius; P, saccus posticus; S, saccus superior; and arrow, site of the cog.



Type A

Type B

Type C

be included in the category of the anterior epitympanic recess. In line with this idea, we recommend that the inferior boundary of this recess should be regarded as the tensor tympanic semicanal, not as the tensor tympanic fold.

Although Proctor[7] did not regard the anterior epitympanic recess as a distinct structure, he recognized a wide space above the tensor tympanic fold in cases in which the attic extended forward through the incisura tensoris and anterior to the tensor tympanic tendon. He used the terms *anterior mallear space* or *anterior compartment of the attic* for such cases. He also used the term *supratubal recess* when the attic extended anteriorly only to the level of the tensor tympanic tendon and the space anterior to the superior mallear fold was in communication with the mesotympanum and eustachian tube. In this instance, he noted that the attic was limited by a medial extension of the superior mallear fold instead of by the tensor tympanic fold, which did not form. However, we consider the boundary mucosal fold as a fusion of the tensor tympanic fold and the superior mallear fold.

As mentioned above, we conclude that the anterior epitympanic recess is a distinct cavity situated anterior to the cog and superior to the tensor tympanic semicanal. This recess is devided into two cavities above and below the tensor tympanic fold. We recommend use of the term *anterior mallear space* for the former and *supratubal recess* for the latter. In type C, the supratubal recess is the same as the anterior epitympanic recess. The anterior mallear recess appears to develop from the anterior saccule of the saccus medius, and the supratubal recess from the saccus anticus. The variations in the shape of the anterior epitympanic recess are probably influenced by the embryologic development of these sacs.

In the surgical management of middle ear diseases, the structural variations of the anterior epitympanic recess must be kept in mind. A sufficient ventilation route from the eustachian tube to the epitympanum can be made by removal of the cog and the tensor tympanic fold in type C. The bony plate to which the tensor tympanic fold attaches should be removed in types A and B. Removal must be accomplished without sectioning the chorda tympani and the anterior mallear ligament.

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Trends in Rehabilitation After Cochlear Implantation

Debara L. Tucci, MD; Paul R. Lambert, MD; Roger A. Ruth, PhD

• Although postimplant rehabilitation is generally considered to be an important aspect of a cochlear implant program, the literature reports widely varying practices in the implementation of such programs. The National Institutes of Health consensus statement on cochlear implantation (May 1988), while recognizing that aural rehabilitation facilitates maximal use of the implant, offers no specific guidelines or recommendations. A questionnaire survey was made of over 200 otolaryngologists to determine current practices in a variety of aspects of their cochlear implant programs. Results were obtained from a total of more than 1400 patients, including adults, adolescents, and children. Rehabilitation is an integral part of the cochlear implant program in the vast majority of active programs surveyed. General aspects of cochlear implant programs as well as those of rehabilitation programs in particular, are discussed.

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Cochlear implantation is now a widely used and accepted method of aural rehabilitation in profoundly hearing impaired adults. While use of the cochlear implant (CI) is widespread, little guidance and some controversy exists in the literature regarding rehabilitation strategies after implantation. The recently published National Institutes of Health consensus report on CIs[1] recognizes the importance of aural rehabilitation directed by a strong interdisciplinary team to facilitate maximal use of the device, but offers no specific recommendations or guidelines.

Opinions expressed in the literature differ widely with respect to rehabilitation strategies. For example, Banfai et al[2] place considerable emphasis on rehabilitation and provide patients with intensive daily therapy over a 4- to 6-week period after implantation. Conversely, Schindler et al[3] report good results from CI recipients after a 30- to 60-minute fitting session with no formal rehabilitation.

The two-stage program developed at the House Ear Institute employs an initial basic guidance program followed by a more lengthy period of auditory training that is tailored to the desires and needs of the CI recipient. The basic guidance program includes orientation on the care and fitting of the CI and basic auditory training, and is estimated to require 20 to 25 hours of patient time.[4]

While implantation has been more controversial in profoundly hearing impaired children than in adults, there is an apparent agreement among professionals that more aggressive therapeutic measures are necessary to insure optimal benefit in this patient group. This is particularly true in the case of prelingually deafened children.

Given the varied approaches reported in the literature, we thought that it would be useful to describe how rehabilitation programs have evolved in existing CI programs in this country. We have defined rehabilitation to include training and instruction in the following: (1) sound awareness (recognition of [novel] auditory signals); (2) visual/auditory processing, including lipreading; (3) speech recognition; (4) mechanical (use of the device and the telephone); and (5) other, including voice, speech, and language therapy.

A questionnaire was devised to inquire about general aspects of CI programs as well as to gather more specific information concerning patient rehabilitation. A separate questionnaire addressed similar issues for children's CI programs. Goals of this study were to obtain information on the demographics of implantation as well as on the relative importance of rehabilitation in existing CI programs, resources devoted to rehabilitation, successful strategies and future directions, and, finally, satisfaction with current CI programs.

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METHODS

The questionnaire used is outlined in Table 1. Categories of responses were given to simplify data tabulation. Respondents were asked to comment on special aspects of their programs that they felt were especially successful. All responses were confidential.

Questionnaires were mailed to a total of 209 individuals or programs. Because of the trend toward development of CI programs in large centers, we elected to send the questionnaire to directors of all residency training programs. In addition, a second list was compiled from other sources, including CI manufacturers. Questionnaires were mailed with a self-addressed stamped envelope. A second mailing was made after 3 months to encourage those who had not yet responded to the initial questionnaire. The second mailing was made in September 1988. Responses were received as recently as April 1989.

RESULTS

General Information

Of the 209 questionnaires mailed, responses were received from 146, or 76%. Eighty-three percent of residency training programs responded, and 56% of the others polled returned the questionnaire. We were nonselective in formulating this list, to be as comprehensive as possible, and believe that it is likely that the majority of those who did not respond do not have CI programs.

Of all programs responding, 99, or 68%, do have an active CI program and have performed implantation on at least one patient. All programs combined reported a total of 1408 CI recipients. Figure 1 illustrates categories of CI recipients according to age at time of implantation and age group at time of hearing loss onset (prelinguistic vs postlinguistic deafness). While the vast majority (73%) of all adults who have undergone implantation lost hearing at a postlinguistic stage, the opposite is true for the children (83% with prelingual deafness). Adolescents make up a relatively small group, with approximately equal numbers of prelingually and postlingually deafened individuals having undergone implantation.

The distribution of implantations performed per program surveyed is illustrated in Fig 2. Half of all implantations, or 704, were performed at the eight largest centers (stippled area). Forty-two percent of all programs have reportedly performed implantations on five or fewer patients. The Nucleus implant is currently used by 70% of all respondents. The next most frequently used device is the House 3-M implant, followed by the Hochmair 3-M, Symbion, and Storz implants.

Queries regarding contraindications to implantation elicited the responses shown in Table 2. Seventeen centers responded to a supplemental questionnaire inquiring about their children's CI program. Adult and children's programs did not differ significantly in patient selection criteria, with the exception that prelinguistic hearing loss was not considered a contraindication to implantation in any children's program surveyed.

Rehabilitation

Personnel devoting time to patient rehabilitation following implantation and time devoted per patient to rehabilitation for both adults and children are illustrated graphically in Figs 3 and 4, respectively. While nearly all programs, both adult and children's, included at least one audiologist on the rehabilitation team, children's programs were more than twice as likely to include also a speech pathologist and/or person trained in auditory rehabilitation.

Figure 4 illustrates that, in three fourths of all children's programs surveyed, personnel spent over 20 hours working with each child following implantation. Typically, fewer hours were spent with each adult recipient. The average amount of time spent in rehabilitation with adult patients was 21.5 (±13.7) hours, compared with 27.3 (±12.2) hours for children. Two thirds of children's programs responding indicated that they spend a considerable amount of time—several, as many as 40 hours or more per child—working with school personnel, including the child's teacher, speech pathologist, vocational counselor, school psychologist, and school administrator.

Respondents from several programs

Table 1.—Questionnaire

- Patient population
  - Age
  - Number implanted
  - Postlinguistic and prelinguistic deafness
- Types of cochlear implants used
- Patient selection
  - Evaluation
  - Criteria for implantation
- Evaluation of postimplantation performance
- Rehabilitation program
  - Personnel
  - Time allocation
  - Special aspects/proposed changes
- Satisfaction with program
  - Program director
  - Percentage of full-time cochlear implant users
- Supplemental questionnaire—children

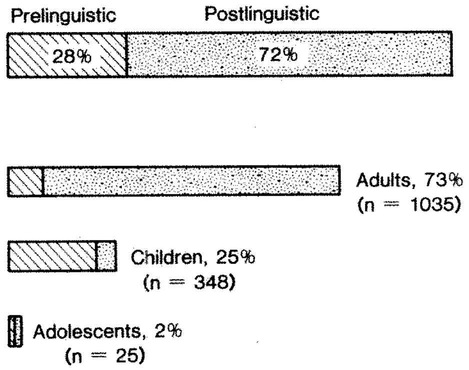

Fig 1.—Classification of cochlear implant recipients (N = 1408) by age at time of implantation and by prelinguistic vs postlinguistic hearing loss.

indicated that the majority of their patients travel long distances to their center, making frequent postimplantation visits impossible. Many indicated that they maintain frequent contact by telephone, attempt in some cases to oversee rehabilitation done elsewhere, and are available for any problems that arise. In some cases, only the surgery is performed by the otolaryngologist at the center surveyed, and all assessment and rehabilitation is carried out elsewhere in the community.

When asked about patient satisfaction and use of the device, respondents indicated that an average of 9 of 10 children and 8 of 10 adults were full-time users of the implant. Lack of patient motivation and family support were most often cited as factors in patient failure to utilize the CI. This was particularly noted to be a problem in the adolescent population.

Lack of available funding for the CI was a source of major concern and frustration for several respondents. This was most frequently a problem for otolaryngologists in solo or small private practice groups, but was also of sufficient concern to preclude establishment of active programs in several of the university departments responding to the questionnaire.

Plans for future changes in the CI programs surveyed most often included establishment of a support group for CI recipients and the addition of a children's CI program.

COMMENT

Since the pioneering work by William House, MD, 30 years ago, the use of the CI for rehabilitation of the profoundly hearing impaired has increased dramatically; 90% of all respondents surveyed began their CI program in the 1980s. Variability has been the rule in dealing with patients who have undergone implantation—variability in ability, educational level, motivation, and social situation. Despite this spectrum, this report demonstrates a uniformity of approach to implantation and rehabilitation in the centers surveyed.

This survey represents the experiences of 99 CI programs in the implantation of more than 1400 patients. The

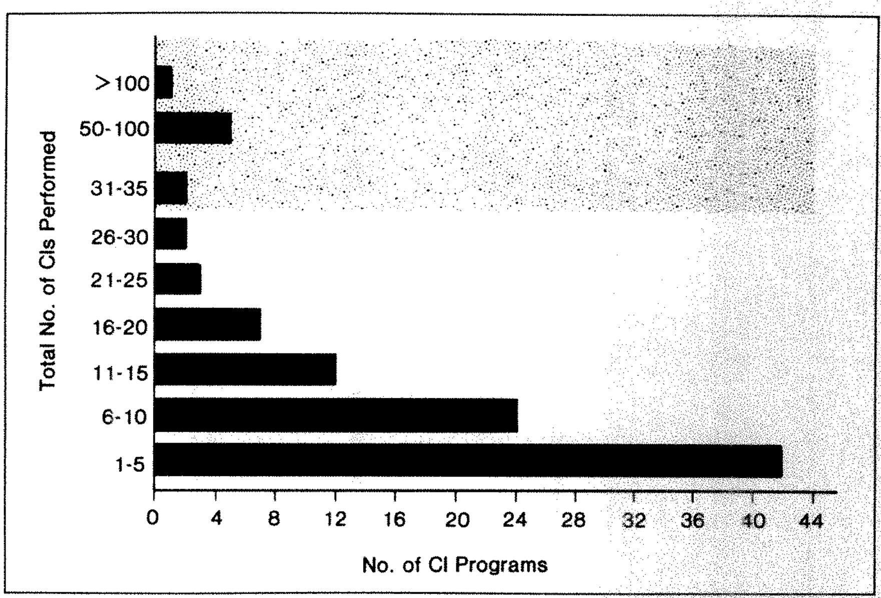

Fig 2.—Distribution of cases among centers surveyed. CI indicates cochlear implant.

Table 2.—Contraindications to Cochlear Implantation

	%	
	Adult	Children
Measurable hearing aid benefit	100	100
Medical	100	100
Psychosocial/educational	83	70
Prelinguistic hearing loss	47	0
Cochlear ossification*	40	35
No response to promontory stimulation†	38	29
Poor lipreading skills	6	(Omitted)

*Observed on computed tomographic scan.
†Age permitting evaluation.

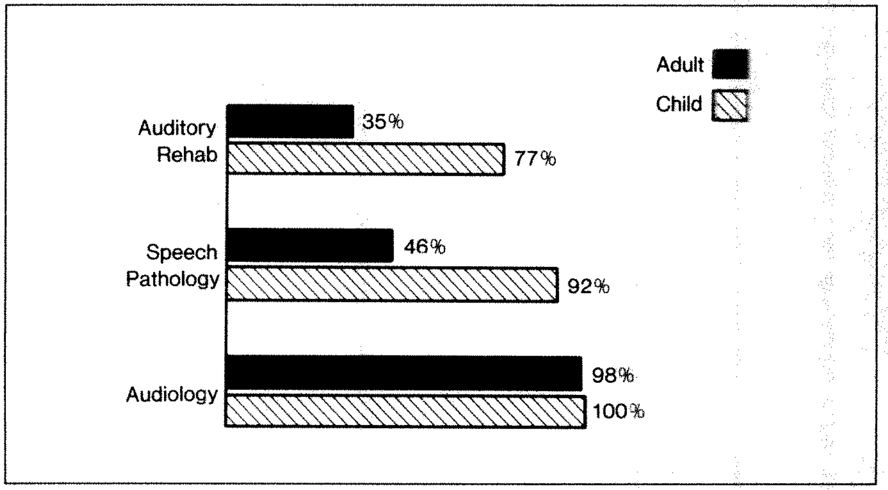

Fig 3.—Professionals included in cochlear implant rehabilitation (Rehab) team for both adult and children's programs surveyed.

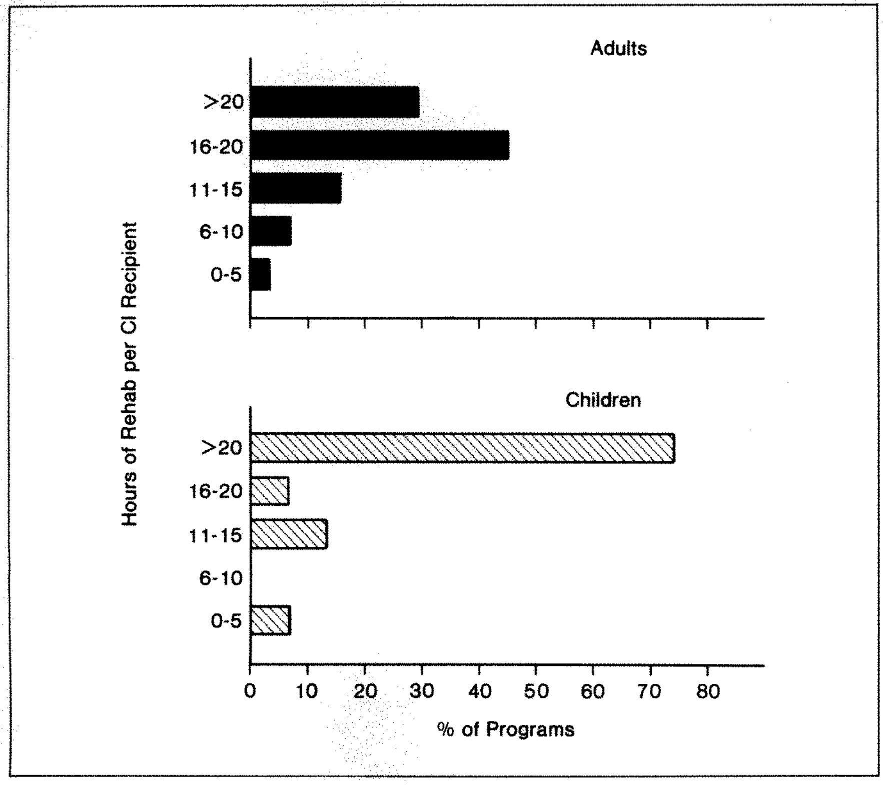

Fig 4.—Hours devoted by center staff to rehabilitation (Rehab) after cochlear implantation for adult and children's programs surveyed. CI indicates cochlear implant.

distribution of cases among these centers is skewed, as more than half of all reported CI recipients underwent implantation at the eight largest centers. Nearly half of all programs responding have performed implantations on five or fewer patients.

Rehabilitation is an integral part of the large majority of these programs. Rehabilitation programs were found to be just as extensive in the smaller programs as in the largest centers surveyed. Only one program director indicated that there is no formal rehabilitation program at that institution.

As expected, implantation in children, the majority of whom are prelinguistically hearing impaired, requires a considerably greater commitment of time and resources from the CI team. Respondents spent an average of nearly 30 hours for rehabilitation with each child, in addition to the many hours spent with professionals who work with the child at home and in the school system. Centers that perform implantations on children are more likely to include a speech pathologist and individuals trained specifically in auditory rehabilitation in addition to audiologists as members of the CI rehabilitation team. Larger centers, and those that perform implantation in children, are more likely to employ individuals to devote their time exclusively to rehabilitation, as opposed to smaller programs in which the same individuals participate in all aspects of the CI program.

A number of respondents utilize services provided by professionals outside their own institution or practice, particularly for rehabilitation after implantation. This seems to be a worthwhile option to in-house rehabilitation, particularly in centers that perform relatively few implantations, or in cases where patients travel long distances to surgical centers.

In summary, rehabilitation following implantation is widely recognized as an essential part of a successful CI program. A variety of options are available to provide for these services. The ultimate responsibility for ensuring that these services are provided rests with the otolaryngologist performing the implantation. All CI recipients are entitled to participate in a rehabilitation program that can provide them with the skills necessary to optimize their use of the device.

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Pulmonary Atelectasis After Reconstruction With Pectoralis Major Flaps

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• Forty-four patients were reviewed to determine the incidence of atelectasis following pectoralis major myocutaneous flap reconstruction of head and neck defects. Patients underwent tumor resection with subsequent pectoralis major myocutaneous flap reconstruction (flap group, n = 24) or another major head and neck procedure (control group, n = 20). Chest roentgenograms taken on the first postoperative day were scored for atelectasis by preestablished criteria. Sixty-five percent of control and 70% of flap patients demonstrated postoperative atelectasis roentgenographically. The flap patients with skin paddles larger than 40 cm² had a 60% incidence of major atelectasis compared with 5% in control patients. The skin island area was strongly correlated with the atelectasis score in the flap group. These results suggest that atelectasis is common following pectoralis major myocutaneous flap reconstruction of head and neck defects. As well, decreased chest wall compliance after primary closure of large donor defects may contribute to the atelectasis observed.

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Atelectasis is the most common postoperative complication and is generally attributed to mechanical ventilation and the attendant pooling of secretions, to hypoventilation secondary to narcotic analgesics, and to splinting of the chest wall to diminish incisional pain.[1-3] Preexisting pulmonary disease and the type of surgery performed are risk factors.[3] After head and neck surgery, the reported incidence ranges from 1% to 5%.[4,5]

The pectoralis major myocutaneous flap (PMMF) has become the "workhorse" of reconstruction following ablative surgery of the head and neck.[6] This flap provides accessible, versatile, and well-vascularized tissue for the primary reconstruction of skin and soft-tissue, intraoral, pharyngeal, or composite defects.[7,8]

Although not mentioned in the surgical literature as a complication, it was our general observation that postoperative atelectasis was relatively common in patients in whom a PMMF reconstruction had been performed. We hypothesized that, in addition to the usual contributory factors, a tight primary closure of the donor site might contribute to atelectasis by restricting chest wall motion. This study was therefore designed to (1) document the incidence of atelectasis following PMMF reconstruction in patients with head and neck cancer and (2) evaluate the effect of flap size on postoperative atelectasis.

MATERIALS AND METHODS

Patient Population

Forty-four patients who had previously undergone resection for squamous cell carcinoma of the head and neck were selected for retrospective review. All surgery had been performed by one of us (P.J.G.). Twenty-four patients had undergone composite resection (n = 23) or laryngectomy (n = 1), with a single PMMF reconstruction of the surgical defect (flap group); 20 patients underwent laryngectomy (n = 19) or radical neck dissection (n = 1) with primary closure (control group). All patients in the flap group had primary closure of the donor site defect; all patients in both groups had tracheostomies as part of their procedure. All patients in both groups were smokers, but individuals with preexisting pulmonary disease were excluded from the study. There was no significant difference in the male-to-female ratio or in the mean ages between the two groups (Table 1). Postoperative chest physiotherapy was performed on all patients.

Data Collection

For all patients in the study, the total anesthesia time and the maximum temperature in the first 24 hours postoperatively were recorded from the medical record. For patients in the flap group, the side of the PMMF and the size of the skin paddle were determined from the operative report.

Table 1.—Patient Data*

Group	N	No. Male	No. Female	Mean Age ± SD, y
Flap	24	16	8	61.0 ± 12.2
Control	20	16	4	60.7 ± 9.2

*No significant flap vs control group differences in male-to-female ratio or mean age.

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Table 2.—Chest Roentgenogram Atelectasis Scores

Atelectasis Evident on Roentgenogram	Score Assigned*
None	0
Single subsegmental	1
Multiple subsegmental	3
Single segmental	3
Mild lobar	2
Moderate lobar	4
Complete lobar	8

*Separate scores were assigned for right and left lungs; the total atelectasis score for that x-ray film was the sum of the scores for the right and left sides.

Table 3.—Atelectasis Categories

Total Atelectasis Score*	Atelectasis Category
0	None
1-5	Minor
>5	Major

*Sum of the scores for the right and left lungs.

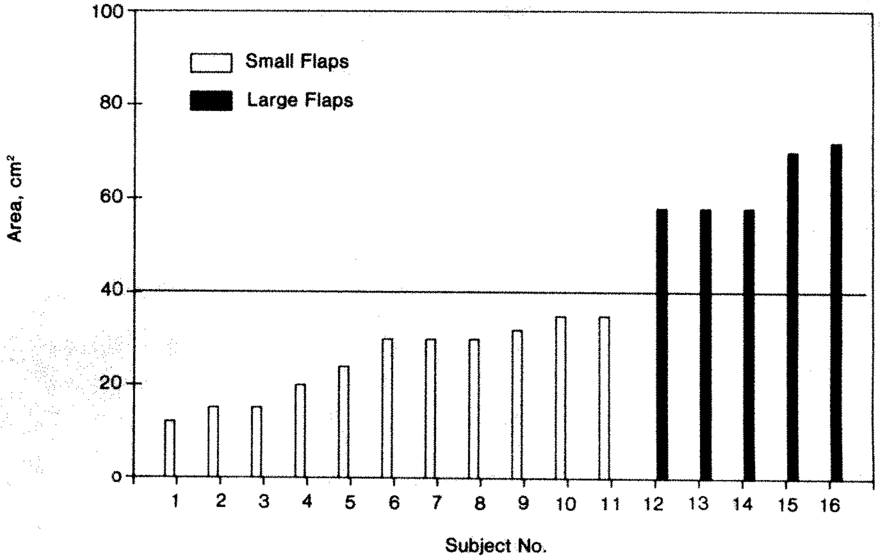

Fig 1.—Bar graph showing the skin island areas for each patient in the flap group. Small skin islands were defined as those with areas less than 40 cm²; big flaps had skin areas more than 40 cm².

The preoperative (posteroanterior and lateral) and day 1 postoperative (portable) chest roentgenograms (obtained routinely by one of us [P.J.G.]) were reviewed by a radiologist who was blinded to the patients' operative procedure. Each roentgenogram was scored for atelectasis according to the breakdown given in Table 2, with the right and left lungs being scored separately. The total atelectasis score for each film was the sum of the scores for the right and left sides. An "atelectasis category" was then assigned for each roentgenogram, as noted in Table 3, so that the statistical analysis would be valid. This scoring protocol has been previously used in similar studies (S.J.H., personal communication, 1988).

Statistical Analysis

Differences in atelectasis category between groups were determined using the χ^2 test for homogeneity. Differences between groups for continuous numerical variables were evaluated using a Student's t test. The Spearman's rank correlation coefficient was used to determine significant relationships between variables. A 5% level of significance was used throughout the study.

RESULTS

The two groups were matched with respect to age and sex as previously noted. The maximum rectal temperature on the first postoperative day was also statistically similar in the flap and control groups (37.3 ± 0.5 vs 37.7 ± 0.5, respectively). There was no atelectasis observed on the preoperative roentgenograms for either the flap or the control patients. A significant difference in mean anesthesia time between the two groups was noted, with the flap patients undergoing 530 ± 81 minutes of general anesthesia vs 411 ± 100 minutes in the control group ($P < .0005$). However, there was no significant correlation between anesthesia time and the postoperative atelectasis score ($r = 0.3$; $P > .05$).

The size of the skin island on the PMMF could be determined from the charts of 16 of the 24 patients in the flap group (Fig 1). To make statistical analysis more valid, flaps were grouped as either "small" or "large" according to whether the skin island was less than or greater than 40 cm², respectively.

The incidence of postoperative atelectasis on the roentgenograms in the control group was 65%, with major atelectasis being noted in 5% of the subjects. The corresponding figures for the flap group were 70% and 25%, respectively. The patients with large flaps had a significantly greater incidence of major atelectasis than either the patients with small flaps or those in the control group (Fig 2). This is reinforced by a highly significant correlation between flap size and total atelectasis score for patients in the flap group ($r = 0.71$; $P < .002$). There was no significant difference in atelectasis between control patients and patients with small flaps.

It should also be noted that there were no significant differences in atelectasis scores between males and females in either group. Last, the side (left or right) donating the pectoralis flap had no effect on the incidence of atelectasis in the right vs left lungs for patients in the flap group. That is, a flap on one side (left or right) does not necessarily mean atelectasis will be worse on the same side.

COMMENT

Our data indicate that 65% to 70% of patients undergoing major head and neck cancer surgery will have roentgenographic evidence of atelectasis on the first postoperative day. The discrepancy between our data and previous studies, which have reported a 1% to 5% incidence of atelectasis following similar surgery,[4,5] is probably due to the criteria used to establish a diagnosis of atelectasis. In those studies, clinical signs and symptoms were used to detect atelectasis in postoperative patients, whereas our study used roentgenographic criteria. In our control group, the incidence of major atelectasis was 5%. If it can be assumed that this "major" atelectasis would be detectable clinically, then this study is consistent with previous reports re-

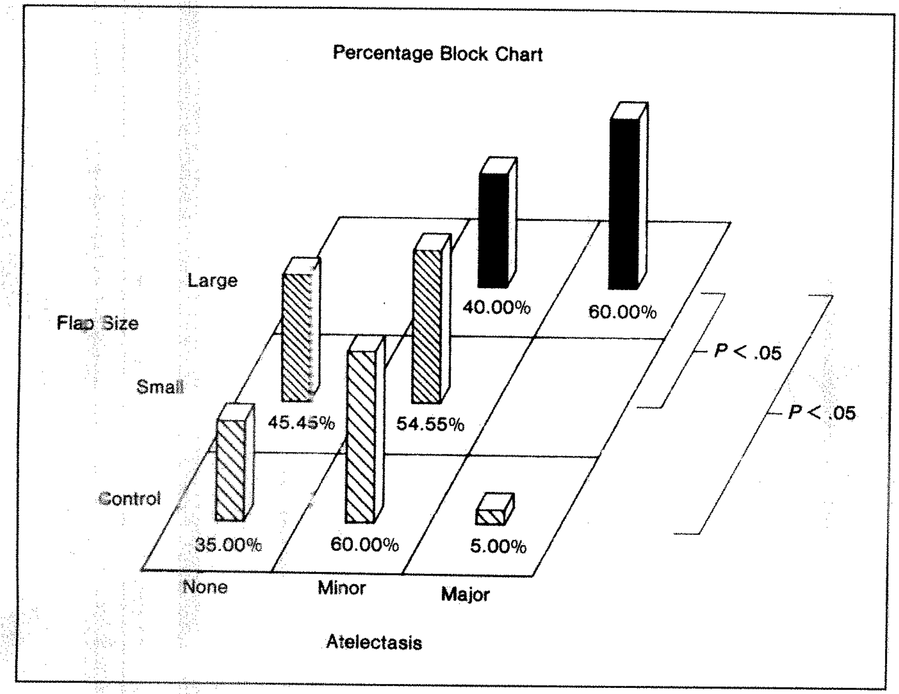

Fig 2.—Atelectasis score category for the flap and control groups according to flap size. Significant differences between groups are noted.

garding the incidence of clinically significant atelectasis following head and neck surgery.

However, the incidence of major atelectasis in patients undergoing pectoralis major flap reconstruction was 25% overall, with a 60% incidence in patients who had flaps with skin island paddles larger than 40 cm². Incisional pain and the accompanying chest wall splinting likely contribute to the increase in atelectasis seen in this group. However, patients with large flaps had a significantly greater occurrence of major atelectasis than either control patients or those with small flaps. This difference, plus the significant correlation between the total atelectasis score and flap size indicates (although it cannot be proven definitively from our study) that the area of the paddle defect probably creates a restriction of chest wall motion from the tight primary closure necessary in the large flap group and that this contributes to an increase in atelectasis seen postoperatively.

In this study, the flap and control groups were well matched for age, sex, smoking habits, and pathologic diagnosis. All patients had tracheostomies and were free of atelectasis or other pulmonary disease preoperatively. The incidence of significant postoperative fever was similar in both groups. Total anesthetic time was significantly longer in the flap group, but there was no correlation between length of general anesthesia and atelectasis for either group. It is therefore unlikely that a confounding variable has influenced these conclusions.

In this retrospective study, the clinical course of the patients regarding the incidence of pneumonia, length of hospitalization, mortality, and so on, was not considered. This was due mainly to inconsistent clinical record keeping between patients and to variable follow-up. For example, a number of patients who had traveled some distance to have surgery in Toronto, Canada, were transferred back to their local hospital early in the postoperative period, with little follow-up. Therefore, it was elected to use an objective criterion (roentgenographic examination) to document postoperative atelectasis in patients who had undergone a major head and neck procedure. Our findings of a high rate of "radiographic atelectasis" and a correlation between skin-paddle size and atelectasis severity in the flap group suggest that further study is warranted. Specifically, a prospective study with standardized clinical data recording and follow-up would allow a correlation between roentgenographic evidence of atelectasis and clinical outcome. In addition, the benefit of specific preventive measures could be evaluated systematically. Preoperative chest physiotherapy, preoperative cessation of smoking, an increased frequency of postoperative chest physiotherapy, and perhaps marcaine injection, epidural anesthesia, or spinal nerve blocks to diminish incisional pain could be appraised as means to prevent atelectasis in the postoperative period.

The results of this study indicate that postoperative atelectasis is a common occurrence in patients who have undergone a pectoralis major myocutaneous flap reconstruction of a head and neck defect. As well, a large cutaneous island on the flap may further predispose the patient to atelectasis via restriction of chest wall motion. Therefore, the prevention, recognition, and treatment of this problem are paramount following this type of surgery. Certainly, all patients should undergo vigorous chest physiotherapy and early mobilization. Because clinical signs may not be manifested until significant atelectasis has occurred, routine postoperative chest roentgenograms may be warranted. Our data indicate that further, prospective study of atelectasis in this group of patients is warranted.

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Split-Palate Approach for Gold Grain Implantation in Nasopharyngeal Carcinoma

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• Although nasopharyngeal carcinoma is radiosensitive, local failure after external radiotherapy is not uncommon and management of persistent or recurrent disease is a therapeutic challenge. The present review reports the use of brachytherapy in the form of gold grain (^{198}Au) implants in the treatment of 23 patients with recurrent or persistent primary nasopharyngeal carcinoma. The split-palate approach was employed in the insertion of the gold grains. This approach allows adequate exposure of the nasopharynx and accurate positioning of the implants. Implantation was successful in 21 patients, and local tumor control was achieved in 17 patients (81%) after a median follow-up of 23 months. Palatal fistula developed in 6 patients (26%): 5 healed with conservative management, and 1 had no functional disturbance. There was no operative mortality, and morbidity of the operation was minimal.

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Nasopharyngeal carcinoma is common in Southeast Asia, with an average annual incidence of 20 cases per 100 000 population.[1,2] Radiation therapy is the most important modality in the treatment of nasopharyngeal carcinoma, but, although the tumor is radiosensitive, local failure in the form of persistent or recurrent tumor is common.[3] The management of local recurrent disease after radical doses of external radiotherapy is a therapeutic challenge. Some centers have advocated further external beam therapy,[4] others have employed brachytherapy.[5,6] The dose of further external radiation is limited by the tolerance of important nearby structures such as the brain stem and the inner ear. Brachytherapy, however, requires adequate exposure of the nasopharynx so that implants can be inserted accurately. A variety of techniques and approaches have been employed to administer brachytherapy, each with its own advantages and disadvantages.[5-7] The present report reviews our experience in employing the split-palate approach for insertion of gold grain (^{198}Au) implants in the treatment of recurrent or persistent primary nasopharyngeal carcinoma.

PATIENTS AND METHODS

Patients

From August 1986 to September 1989, in the Department of Surgery, University of Hong Kong and the Institute of Radiotherapy and Oncology, Queen Mary Hospital, Hong Kong, brachytherapy was employed in the management of 23 patients (16 men, 7 women) with carcinoma localized in the nasopharynx. The median age of the patients was 45 years (range, 30 to 65 years). All 23 patients had received radical courses of external radiation therapy, the dosage ranging from 5520 to 6100 cGy, with a median of 5950 cGy. Before radiotherapy, the tumor size and lymph node metastasis status were classified using Ho's staging system.[8] Seven patients had stage I disease; 5, stage II; 6, stage III; and 4, stage IV. One patient had radiotherapy treatment elsewhere, and his preradiotherapy clinical stage was not available. The extent of primary tumor and the lymph node involvement of the 22 patients are listed in the Table. Of the whole group of 23 patients, 14 had recurrent carcinoma and the other 9 had persistent tumor in the nasopharynx despite radical radiotherapy. All 23 patients had T1 disease, as their tumor was localized in the nasopharynx. None had lymph node metastasis. Patients with extensive disease were not included.

Computed tomography was performed on all patients before they underwent the initial radical radiotherapy. However, before brachytherapy, the tumor was clinically larger than 1 cm in diameter in 8 patients. Computed tomography was performed on these patients to determine the extent of tumor before the implantation of the gold grains (Fig 1).

Two of the 14 patients with recurrent nasopharyngeal carcinoma after external radiotherapy initially had their recurrence

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managed successfully with intracavitary radiation in the form of cesium intubation. The tumors in these 2 patients recurred again locally and were managed with gold grain implants. The disease-free interval between the last radiation treatment and the presenting recurrence in these 14 patients ranged from 21 to 183 weeks, with a median value of 62 weeks.

Tumor Extent and Lymph Node Status of 22 Patients Before Radical Radiotherapy*

	N0	N1	N2	N3	No. of Patients
T1	7	2	4	2	15
T2	1	2	0	0	3
T3	0	0	2	2	4

*Classified according to Ho's staging system.[8] The information was not available for 1 of the 23 patients included in the study.

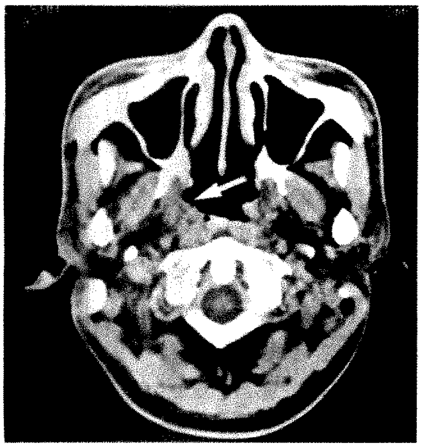


Fig 1.—Computed tomographic scan of recurrent nasopharyngeal carcinoma (arrow) for assessment of extent of tumor before brachytherapy.

Of the nine patients who had residual disease in the nasopharynx after radical radiotherapy, the interval between the completion of initial radiation and their brachytherapy ranged from 3 to 10 weeks, with a median of 4 weeks.

Operative Technique

The implantation of radioactive gold grains (^{198}Au) was performed with the patient under general anesthesia in the supine position. A Dingmann's mouth gag was introduced and the palate exposed. In patients with trismus, the interalveolar distance could be stretched after induction of anesthesia, and as long as the dental gap was more than 3 cm, the operation could be carried out.

Ten milliliters of saline containing 1:100 000 adrenaline was injected submucosally along the planned incision over the palate. The incision started from one side of the uvula and was extended along the midline of the whole soft palate to a point halfway up the mucosa covering the hard palate (Fig 2). The soft palate was completely divided and retracted laterally, and the mucoperiosteum over the hard palate was elevated and retracted. In this way, the tumor in the nasopharynx was exposed (Fig 3). When the tumor had extended to the anterior part of the roof of the nasopharynx, a part of the bone of the hard palate could be removed for exposure. The size of the tumor was then obtained by measurement, and this in turn determined the number of gold grains that would be required. The radioactive gold grains (^{198}Au) were inserted with a specially designed introducer (Royal Marsden Gold Grain Implantation Gun MKIII) under direct vision. As each gold grain implant was expected to irradiate tissue within 0.5 cm, a plastic flange was cuffed around the barrel of the gun at a distance of 0.5 cm from the tip. This flange would determine precisely the depth of insertion of the gold grain from the mucosal surface (Fig 4). Bleeding from the tumor was usually controlled with a small piece of Surgicel (Ethicon, Edinburgh, Scotland). A piece of lead shield tied with a silicon loop to one end was then laid on the implanted site in the nasopharynx to reduce the radiation exposure to the surgeon's fingers (Fig 5). The long silicon loop facilitated removal of the shield behind the closed palatal wound at the end of the operation. The palate was then closed with interrupted sutures. For the first 10 patients, the closure was done with one-layer through-and-through suturing, but for the subsequent 13 patients the palatal wound was closed with three layers of interrupted polyglactin 910 (Vicryl) (Fig 6).

During the surgical closure of the palatal wound, a horseshoe-shaped lead shielding was placed around the patient's head to reduce the radiation exposure to the surgeon and his assistants. A piece of lead glass was mounted on the shield, which also reduced radiation exposure to the surgeon's eyes (Fig 7). After closure of the palatal wound, the lead shield in the nasopharynx was removed from behind the soft palate by pull-

Fig 2.—Incision over the midline of the soft palate. Starts from one side of the uvula and ends midway up the hard palate.

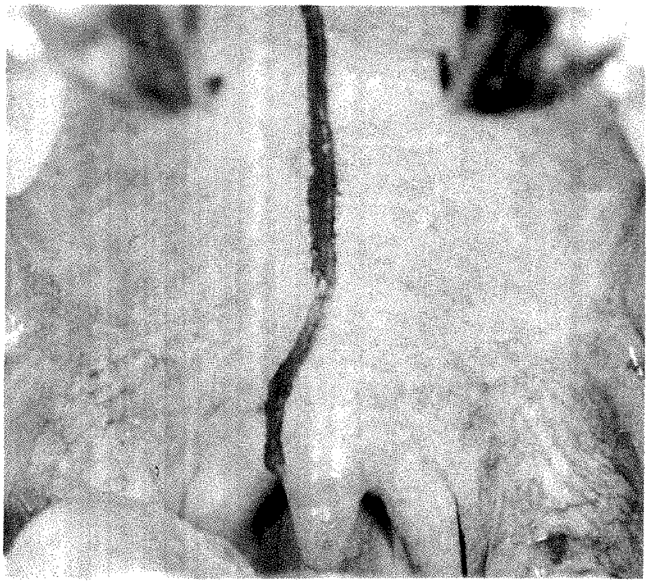
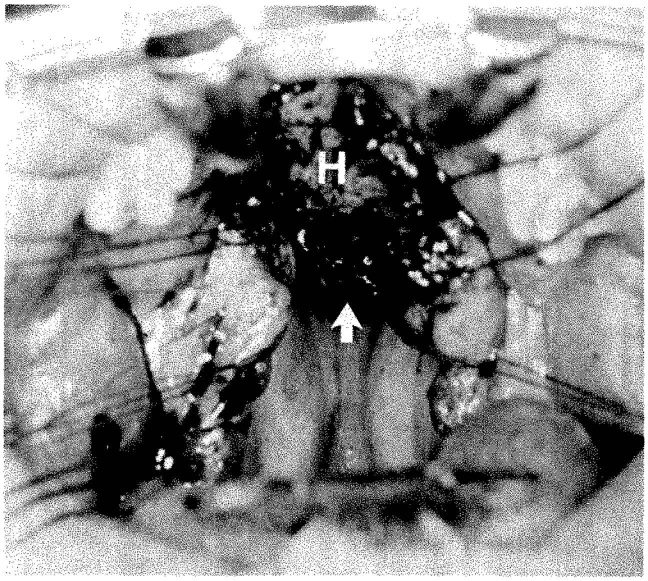


Fig 3.—Divided soft palate and mucoperiosteum over the hard palate (H) were retracted laterally to expose the tumor in the nasopharynx (arrow).



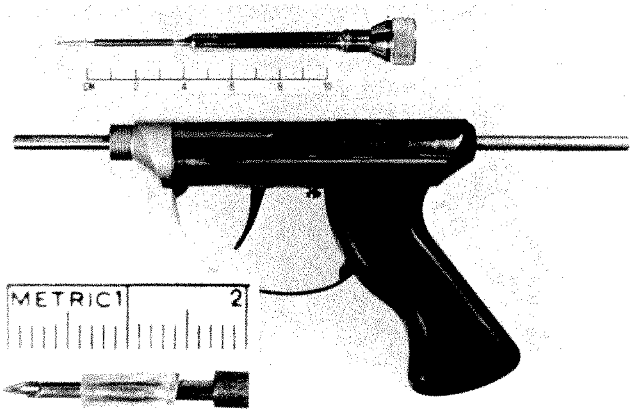


Fig 4.—Gold grain implantation gun. Inset, Plastic flange on barrel used to determine the depth of implantation.

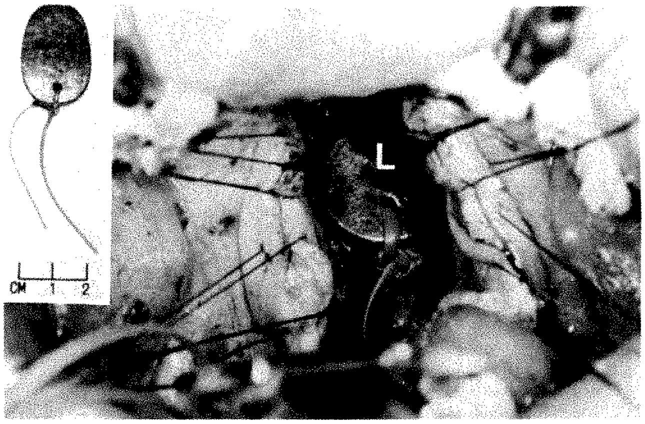


Fig 5.—Lead shield (L) covered the nasopharynx after gold grain implantation. Inset, Lead shield with long silicon loop ends.

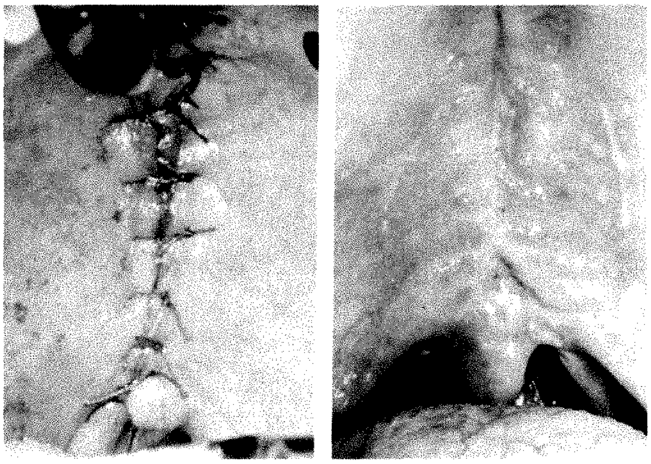


Fig 6.—Left, Closed palatal wound. Right, Completely healed palatal wound 2 months after operation.

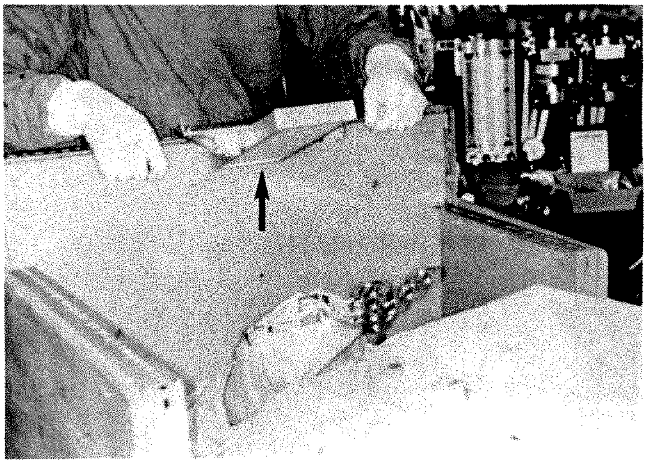


Fig 7.—Horseshoe-shaped lead shield with mounted lead glass (arrow), placed above the patient's head to protect the surgeon and assistants.

ing on the silicon loop. The patient was usually allowed oral intake of fluids the next day and was discharged home on the fourth day after the operation.

RESULTS

The size of the recurrent tumor in the 23 patients ranged from 0.5 to 2 cm in diameter, and the number of gold grain implants varied from 4 to 14 (Fig 8).

In all 23 patients, exposure of the nasopharynx was adequate. The dental gap ranged from 3 to 8 cm, with a median of 6 cm. In seven of the 23 patients, part of the hard palate was removed to improve exposure.

In 2 of the 23 patients, the implanted gold grains were dislodged in the early postoperative period. In one patient, 6 of the 10 implanted gold grains were dislodged and 2 of them were swallowed (Fig 9). In another patient, 9 of the 10 gold grains were discovered in the expectorant. These, however, caused no problems.

Six (26%) of the 23 patients developed a palatal fistula (Fig 10); 5 of these were among the 10 patients whose palatal wounds were closed with one layer of through-and-through sutures. When the palatal wound was closed with three layers of sutures, only 1 of 13 patients developed a fistula. Five of the six fistulas healed without active management. The remaining patient wore a dental plate initially, and the fistula contracted to pinhole size. He had no functional disabilities.

The 21 patients who had a successful implantation of gold grains were followed up from 6 to 36 months (median, 23 months). Four patients developed local recurrent tumor, but the other 17 patients remained free of local disease. Of the 17 patients with local control, 5 developed distant metastases: 2, in the lung; 2, in the spine; and 1, in the neck. The remaining 12 patients had no evidence of disease with a median follow-up of 27 months (range, 10 to 32 months). The actuarial survival rate of the 21 patients at 3 years was 64% (Fig 11).

COMMENT

Although nasopharyngeal carcinoma is a radiosensitive tumor, persistent or recurrent tumor at the primary site is not uncommon.[3,9] The treatment of such disease is far from satisfactory.

The treatment of locally recurrent nasopharyngeal carcinoma is possible either by further doses of external ra-

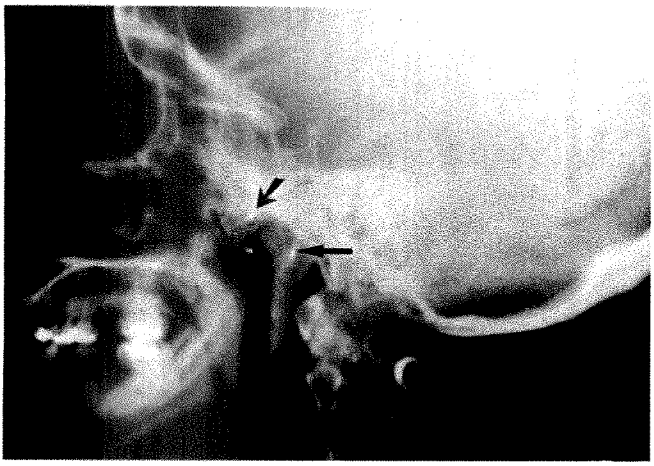


Fig 8.—Lateral roentgenogram of the skull showing the gold grains (arrows).

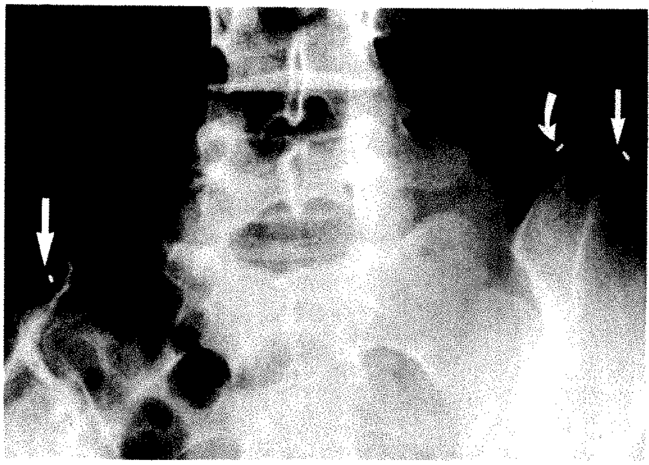


Fig 9.—Abdominal roentgenogram showing the swallowed gold grains (arrows).

diotherapy or by brachytherapy. External irradiation in the treatment of recurrent or persistent local disease may produce a few survivals and provide long-term palliation,[4] but it has its limitations. As the recurrent or persistent local disease is probably due to the relative radioresistance of the tumor, the second dose of radiation needs to be greater than the primary dose. The nasopharynx is surrounded by important structures that limit not only the irradiation dose but also the application of external radiation fields. Neuroendocrine and soft-tissue damage is not uncommon with a second dose of external radiotherapy.[10,11]

Brachytherapy, on the other hand, has the advantage of giving a high dose of radiation energy to the target tumor while delivering a much lower dose to adjacent normal tissues.[12] As the local recurrent or persistent nasopharyngeal carcinoma is usually of small volume, larger doses of radiation can safely be given, and it is possible to achieve eradication of the tumor when the amount of radiation administered is adequate.[13]

Intracavitary brachytherapy, in the form of cesium intubation, although simple to introduce,[14] is difficult to maintain in the planned position to achieve an adequate tumoricidal dose. Gold grain (^{198}Au) implants can be inserted directly into the bulk of the tumor and its adjacent tissue. The dose of radiation used to treat the tumor can be accurately controlled. As the radiation dose of a gold grain falls off rapidly with increasing distance from the grain, its effect on normal brain, the pituitary gland, or the inner ear is minimal. The effective tumoricidal range of a gold grain (^{198}Au) implant is only about half a centimeter; therefore, it must be inserted accurately into the desired depth to maximize its full efficiency. It is not ideal to treat large volumes of tumor tissue; thus, patient selection has to be stringent. All of our patients underwent preimplantation computed tomography of the nasopharynx and neck to ascertain that recurrence was localized in the nasopharynx.

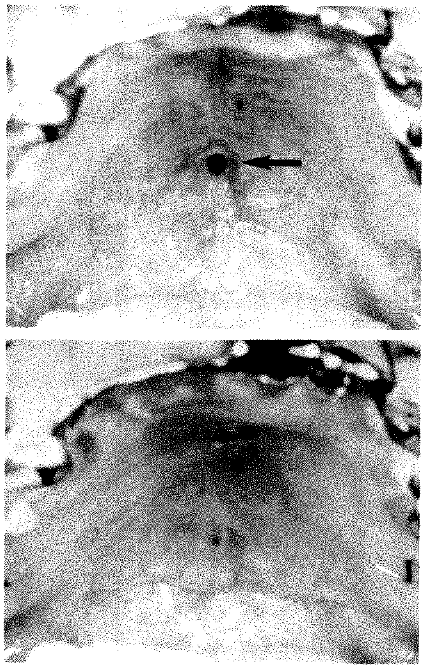


Fig 10.—Top, Palatal fistula (arrow). Bottom, Fistula covered completely by dental plate.

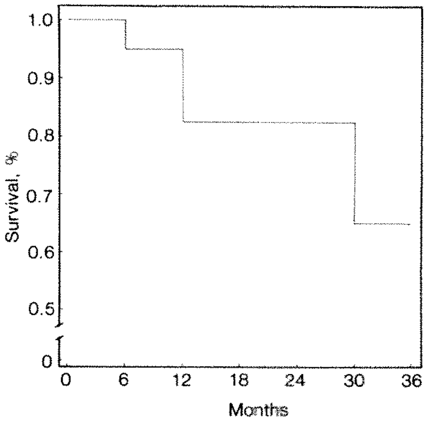


Fig 11.—Actuarial survival curve for 21 patients who had successful implantation of gold grains.

Carcinomas in the nasopharynx can be approached via the transpalatal route[15] or the infratemporal fossa route.[16] The transpalatal approach gives adequate exposure of the whole nasopharynx; whereas the latter necessitates a more extensive dissection, and an external scar is inevitable. The palatal incision usually described for nasopharyngeal exposure is a U-shaped incision along the medial border of the upper gingival ridge. A mucoperiosteal flap, based posteriorly, is then elevated off the entire hard palate. The posterior part of the hard palate is then removed to expose the tumor in the nasopharynx. This technique provides exposure of the nasopharynx, but palatal bone has to be removed in all patients. When the recurrent tumor involves the posterior wall of the nasopharynx, the posteriorly based mucoperiosteal flap prevents adequate exposure of the lower limit of the tumor. It also hinders the free movement of the tip of the gold-grain insertion gun and thereby prevents accurate placement.

We elected, therefore, to place the incision along the midline of the palate. The two palatal flaps could then be retracted laterally to give adequate exposure of the entire tumor in the nasopharynx. When the tumor has extended to the roof of the nasopharynx, part of the hard palate has to be removed to expose the upper limit of the tumor. This additional procedure was necessary in 7 of the 23 patients in the present study and did not give rise to increased morbidity. The laterally retracted palatal flaps did not hinder the movement of the gun; therefore, accurate insertion of gold grains was possible.

One disadvantage of an interstitial implant is the radiation hazards that may affect the surgeon, the radiotherapist, and the operating room staff. The insertion of the lead plate into the nasopharynx before closure of the palate and the placement of the horseshoe-shaped lead shield reduce radiation exposure to operating room staff. The maximal dose to the trunk and fingers of the surgeon is less than 0.015 and 0.05 cGy, respectively, per implant of eight gold grains.

One problem that we have encountered during the procedure is dislodgment of the inserted gold grains. We found that this was related to the technique of insertion and to the consistency and thickness of the tissue in the nasopharynx. The thickness of tumor and adjacent nasopharyngeal tissue can be determined by computed tomographic scan before the implantation. At the time of insertion, the operator should insert the tip of the gun well into the target tissue before firing to extrude the gold grain. After the implantation of a gold grain, the tip of the gun should be withdrawn slowly to allow tissue recoil to keep the gold grain in position. After all the gold grains had been implanted in our patients, a small piece of Surgicel (Ethicon) laid over the nasopharynx was adequate to control any oozing of blood. Suction, diathermy coagulation, and any other manipulation that might displace the grains should be avoided. Usually, dislodged gold grains would be discovered in the expectorant of the patient in the postoperative period. One of our patients swallowed three of the dislodged gold grains. This did not produce any consequence and did not cause any discomfort. The gold grains were passed in the feces 3 days later.

Another problem that was frequently encountered initially was nonhealing of the palatal wound. The most frequent site for breakdown was where the soft palate musculature joined the posterior edge of the hard palate. It is probable that this was the site where tissue mobility was the greatest. Five of the six patients who developed a palatal fistula belonged to the first group of patients, whose palates were closed with one layer of absorbable sutures. When the palate was closed in three layers, only 1 of the 13 patients developed palatal wound breakdown. Previous external radiotherapy and the amount of radiation dose from the implanted gold grains also probably contributed to the poor healing of the wound. The patient who developed a palatal fistula despite a three-layer closure had 14 gold grains implanted.

Once a palatal fistula has developed, it causes a lot of inconvenience to the patient. The voice assumes a nasal tone, and oral intake of food and fluid is regurgitated through the nose. Both of these disturbances can be prevented by a dental plate (Fig 10). Healing can be expected with conservative management; five of the six palatal fistulas in our patients healed completely. Even when healing was incomplete in the last patient, the fistula contracted to pinhole size and did not cause any inconvenience to the patient. He does not require a dental plate.

The local disease control rate in the present series was 81% after a median follow-up of 14 months. This local control rate is higher than that achieved with other treatment modalities for recurrent or persistent primary nasopharyngeal carcinoma.[14] The morbidity associated with the operation and implantation is low and acceptable. Although it is too soon to assess the long-term results of this procedure, the early results are certainly promising. We would recommend it for patients who suffer from recurrent or persistent carcinoma in the nasopharynx after external radiotherapy.

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β-Tubulin Epitope Expression in Normal and Malignant Epithelial Cells

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• The expression of a unique β-tubulin isoform (class III) was monitored in squamous cell carcinoma (SCC) and normal epithelial cells using a monoclonal tubulin antibody called TuJ1. Whole tissue homogenates of SCC, normal tissue, SCC grown in nude mice, and SCC cultured cells were examined using sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western blot. TuJ1 antibody localization was performed using peroxidase immunostaining on paraffin sections of SCC, normal tissue, nude mouse SCC, and immunofluorescent microscopy of SCC cultured cells. The malignant tissues examined stained positive with TuJ1 and a general β-tubulin antibody, whereas the normal tissues stained positively only for the general β-tubulin antibody. TuJ1 epitope expression may be a useful marker for SCCs and may assist in understanding differences between normal and malignant squamous cells.

***(Arch Otolaryngol Head Neck Surg.* 1990;116:583-589)**

Like all nucleated cells, cancer cells normally possess a network of microtubules. These cytoskeletal structures are hollow, 25-nm (diameter) cylinders of indefinite length.[1] Microtubules are involved in maintenance of cell shape, movement of chromosomes, movement of cilia and flagella, secretion, and movement of intracellular particles.[2] Microtubules consist of a protein heterodimer composed of one α and one β subunit. In mammalian cells, a variety of tubulin isotypes result from the expression of multiple tubulin genes[3-5] and from posttranslational modifications.[6-8] These isotypes are classed by the carboxy-terminal sequences of the peptides coded by the different genes and by their tissue distribution.[9-11] There is variation in the expression of the various isotypes during differentiation and development.[8,12-15]

It is possible that the expression of a different combination of isotypes contributes to the diversity of microtubular functions, but there is little conclusive evidence to support this hypothesis. While different isotypes have not been shown to have functionally specific roles, there is evidence that they vary in polymer stability,[6] rates of assembly,[16,17] and ability to bind to small ligands.[18]

In this study, the expression of a class-III β-tubulin,[15,19-22] which is recognized by a monoclonal antibody TuJ1, is examined in normal and malignant oral epithelial tissues in an attempt to understand how variations in microtubule composition might correlate with the malignant state and serve as markers for malignant epithelial cells.

MATERIALS AND METHODS

Sodium Dodecyl Sulfate (SDS) Polyacrylamide Gel Electrophoresis (PAGE) and Western Blotting Procedure

Tissue culture samples for Western blot analysis were obtained by scraping the cells from six confluent 75-cm² flasks in 1 mL of 1× Laemmli sample buffer.[23] Samples were sonicated four times for 1 second with a Branson Sonifier 450 (Branson Ultrasonics Corp, Danbury, Conn) set at 20% of the duty cycle, and centrifuged for 8 to 10 minutes at 15 600g to remove DNA and any insoluble material. Protein analysis of the resulting cell extracts was performed using a modification of the standard Lowry procedure.[24]

Tissue homogenates were prepared by adding 0.1-mol/L imidazole plus 1-mmol/L phenylmethylsulfonylfluoride in a 1:1 weight-to-volume ratio. The tissue was minced, homogenized in an ice-water bath for 2 minutes at approximately 600 rpm, and centrifuged for 30 minutes at 40 000g at 4°C. An equal volume of 2× Laemmli sample buffer was added to the supernatant and boiled for 3 minutes.

Proteins were separated by SDS PAGE using a modification[25] of the method of Laemmli.[23]

The gels contained a 4% to 16% acrylamide gradient and a 3% to 6% urea gradient. The proteins were transferred to nitrocellulose by the method of Towbin et al.[26] The nitrocellulose was washed with phosphate-buffered saline (PBS) (or 0.01-mol/L TRIS-saline; pH 7.4) and blocked in PBS containing 0.1% polysorbate (or TRIS-saline in 5% nonfat dry milk). Individual strips were incubated overnight at 4°C with the appropriate primary mouse monoclonal antibody. Dilutions used were as follows:

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Reprint requests to the Department of Otolaryngology-Head and Neck Surgery, University of Virginia Health Sciences Center, Box 430, Charlottesville, VA 22908 (Dr Levine).

TuJ1 (growth supernatant; 1:5000), Tu9B (growth supernatant; 1:2500), and Tu-α (ascites fluid; 1:20 000). Following four washes, the nitrocellulose strips were incubated with goat anti-mouse IgG peroxidase conjugate (1:10 000; Hyclone Laboratories Inc, Logan, Utah) and washed four times. All washes and dilutions were performed using PBS-polysorbate 20 (or TRIS-milk). The nitrocellulose strips were placed in a solution of 0.05-mol/L Trizma-7.6 (Sigma Chemical Co, St Louis, Mo), 0.01-mol/L imadizole, 1-mmol/L diaminobenzidine, and 0.0075% hydrogen peroxide for color development. The strips were washed with distilled water and immediately photographed on 35-mm film (Kodak Pan-X or technical pan) using a blue filter. The nitrocellulose strips were then dried and rephotographed.

Cell Culture

Squamous cell carcinoma (SCC) lines UM SCC 17A, UM SCC 17B, and UM SCC 38 were obtained. The cells were grown in Eagle's Minimum Essential Medium supplemented with 1% nonessential amino acids, 2-mmol/L glutamine, and 15% fetal calf serum at 5% carbon dioxide.

Nude Mouse Implants

The SCC tumor implantation followed a procedure previously described.[27] Tissue removed from the nude mice either was formaldehyde-fixed and embedded in paraffin or frozen and stored at −80°C until analyzed.

Surgical Removal of Tissue Biopsies

Biopsy specimens of normal mucosa or SCC biopsy specimens were taken from patients' orohypopharynx or oral cavity after local anesthesia using 1% xylocaine with epinephrine or under general anesthesia during the staging endoscopy procedure. All the patients signed a consent form approved by the Human Investigation Committee of the University of Virginia Health Sciences Center, Charlottesville. The samples were immediately placed in plastic containers, labeled, and immersed in liquid nitrogen to await future analysis.

Peroxidase Immunocytochemistry

Six-micrometer-thick sections of formalin-fixed, paraffin-embedded tissue were placed on gelatin-coated slides. Following deparaffinization, the sections were immunostained as described for monoclonal antibodies in previous work.[22] The primary antibody dilution for the TuJ1 and Tu9B antibodies was 1:1000 (growth supernatant). Withholding primary antibody and substituting a mouse monoclonal antibody to a flagellar membrane glycoprotein were used as negative controls to verify the specificity of the staining. Photographs were taken on a microscope (Leitz Ortholux II) using 35-mm film (Fujicolor ASA 100).

Immunofluorescent Staining

Cultured cells were plated onto sterile coverglasses, fixed in cold methanol for 10 minutes, and rehydrated in PBS. For fluorescein labeling, the coverglasses were first incubated for 30 minutes in 5% bovine serum albumin, followed by 30 minutes in 5% normal goat serum and an overnight incubation at 4°C in primary antibody. TuJ1 and Tu27 growth supernatants were both diluted to 1:200. Substituting a flagellar membrane glycoprotein monoclonal antibody and witholding primary antibody produced slides that were used as negative controls. The coverglasses were then washed three times and incubated at 37°C for 2 hours in fluorescein isothiocyanate-labeled goat anti-mouse IgG antibody diluted to 1:20. Following three additional washes, the coverslips were mounted on a slide using 10× PBS diluted to 1:10 with glycerol plus 0.4% *n*-propylgallate to retard fluorescent bleaching. All washes and dilutions were performed using 1% normal goat serum and 0.5% bovine serum albumin in PBS.

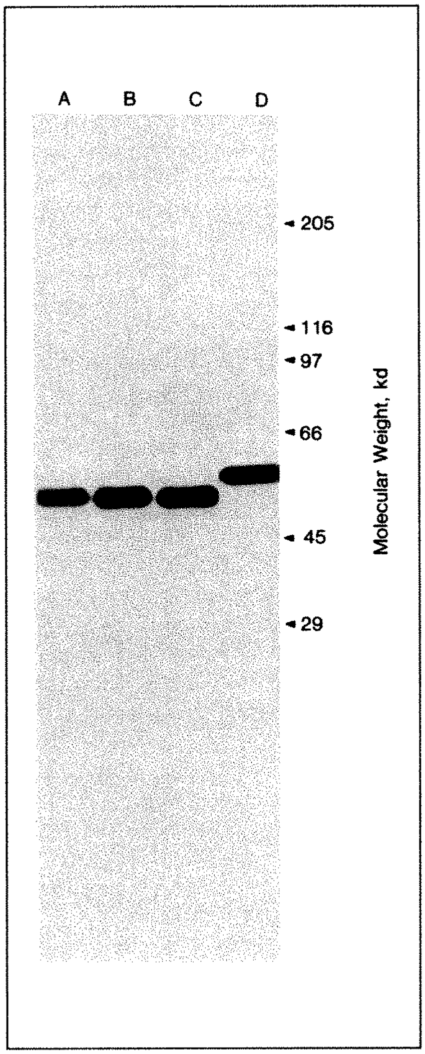


Fig 1.—Western blot of phosphocellulose purified rat brain tubulin stained with the monoclonal antibody TuJ1 to class-III β-tubulin isotype (lane A), general β-tubulin monoclonal antibodies Tu9B (lane B), and Tu27 (lane C), and a general α-tubulin monoclonal antibody Tuα (lane D).

Texas Red immunofluorescence followed the above procedure up to the 2° antibody step. At this point, the coverglasses were incubated in biotin-labeled sheep anti-mouse IgG antibody (1:25; Amersham Corp, Arlington Heights, Ill) for 45 to 60 minutes, washed, incubated in Texas Red streptavidin (1:25; Amersham) for 15 to 30 minutes, washed, and mounted in PBS/glycerol. Pictures were taken on a microscope equipped with epifluorescence optics using 35-mm film (Kodak Tri-X).

RESULTS

The mouse monoclonal antibodies Tu9B and Tu27[28] recognize all β-tu-

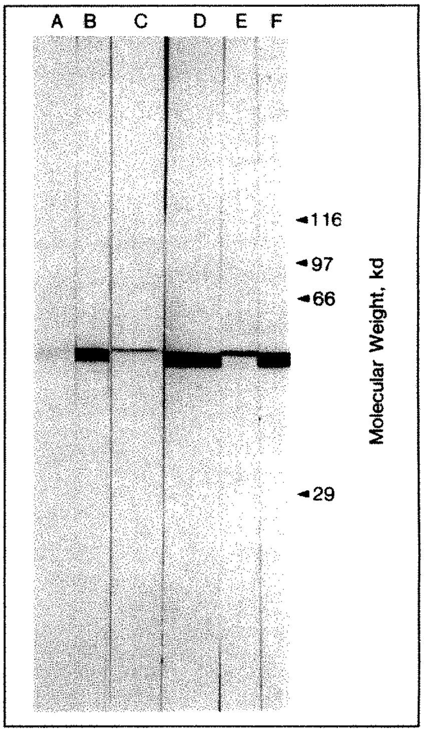


Fig 2.—Western blot of normal oral mucosa (lanes A and B, 400 μg of protein) and squamous cell carcinoma homogenates (lanes C and D, 100 μg of protein; lanes E and F, 400 μg of protein) from the same individual stained with the TuJ1 antibody (lanes A, C, and E) and with the Tu9B antibody (Lanes B, D, and E).

bulin isotypes. The monoclonal antibody TuJ1 recognizes a class-III β-tubulin isotype that has been reported to be primarily neuron-specific, although it also cross-reacts with the testis.[15,19-22] Figure 1 shows a Western blot of phosphocellulose purified rat brain tubulin separated by SDS PAGE. Lane A is stained with the TuJ1 antibody, lane B is stained with the Tu9B antibody, lane C is stained with Tu27 antibody, and lane D is stained with Tuα antibody, a general monoclonal antibody for α-tubulin. TuJ1, Tu9B, and Tu27 stain the β-tubulin band at 54 000 d, and Tuα stains α-tubulin at 56 000 d.

TuJ1 stains malignant epithelial tissues derived from human squamous cell carcinomas, but does not stain corresponding normal tissue (oral mucosa). Figure 2 shows Western blots of tissue homogenates separated by SDS PAGE from both normal human epithelial tissue (lanes A and B) and a human SCC (lanes C through F). Both samples are from the same patient and are recognized by the broad-spectrum β-tubulin antibody Tu9B (lanes B, D, and F). The normal epithelial tissue, even at a protein load of 400 μg (lane A), does not bind the TuJ1 antibody. The SCC tissue stains with TuJ1 at protein loads of both 400 (lane E) and 100 μg (lane C). Lanes C and E show a slightly slower migration of the β-tubulin recognized by TuJ1 relative to the β-tubulin recognized by Tu9B. This slower migration of the TuJ1 epitope may reflect a slightly different apparent molecular weight.

Table 1 lists the results of Western blot staining of the various tissue homogenates with the TuJ1 antibody. The TuJ1 antibody recognized 14 human squamous cell tumors. None of the 10 normal human epithelial tissue homogenates reacted with the TUJ1 antibody, including 4 normal tissue specimens obtained from patients who were donors of TuJ1-positive SCC tissue. All normal tissue homogenates were recognized by the general β-tubulin monoclonal antibody (Tu9B). Several nonepithelial human tumors listed in Table 1 also gave a positive reaction with both the general β-tubulin antibody Tu9B and the TuJ1 antibody.

Immunocytochemistry of tissue sections confirmed the presence of TuJ1 staining in SCC tissue and its absence in normal mucosa (Color Fig 1). Both normal and malignant cells exhibit the brown diaminobenzidine reaction product after staining with the general β-tubulin antibody Tu9B (Color Fig 1, a and b). Only the tumor cells demonstrated positive staining with the TuJ1 antibody (Color Fig 1, d). Positive staining with TuJ1 antibody was also present in tumor cells that were dividing (example not shown). The normal squamous cells did not stain with TuJ1 (Color Fig 1, c). Occasional profiles of nerves seen in the normal oral mucosal tissue exhibited positive staining with the TuJ1 antibody (example not shown). Antibody controls for both SCC and normal tissue demonstrate low background staining (Color Fig 1, e and f).

Table 1.—Western Blot Results From Whole Tissue Homogenates

	No. Positive/No. Tested	
Tissue Type	**TuJ1 Expression**	**Tu9B Expression**
Squamous cell carcinoma	14/14	14/14
Normal oral mucosa	0/10	10/10
Esthesioneuroblastoma	3/3	3/3
Lymphoma	2/2	2/2
Aggressive fibromatosis	1/1	1/1
Malignant melanoma	1/1	1/1

Table 2.—Western Blot Results From Squamous Cell Carcinoma Tumors Grown in Nude Mice

Tissue No.	TuJ1 Expression	Tu9B Expression
073086AI*	+	+
073086BI	+	+
101586AI*	+	+
030587AII	+	+
042287AI	+	+
051387AI	+	+
062587AI	+	+
072887AI	−	+
072386AII	+	+
080886I*	+	+

*Tumors selected for study using immunocytochemistry.

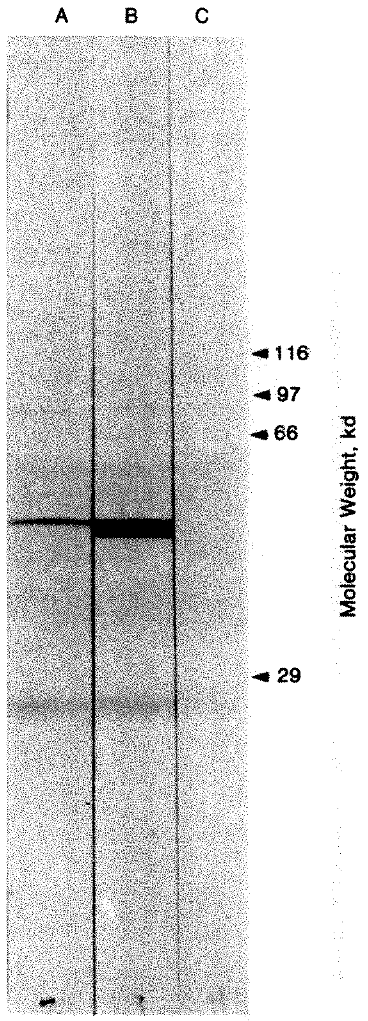
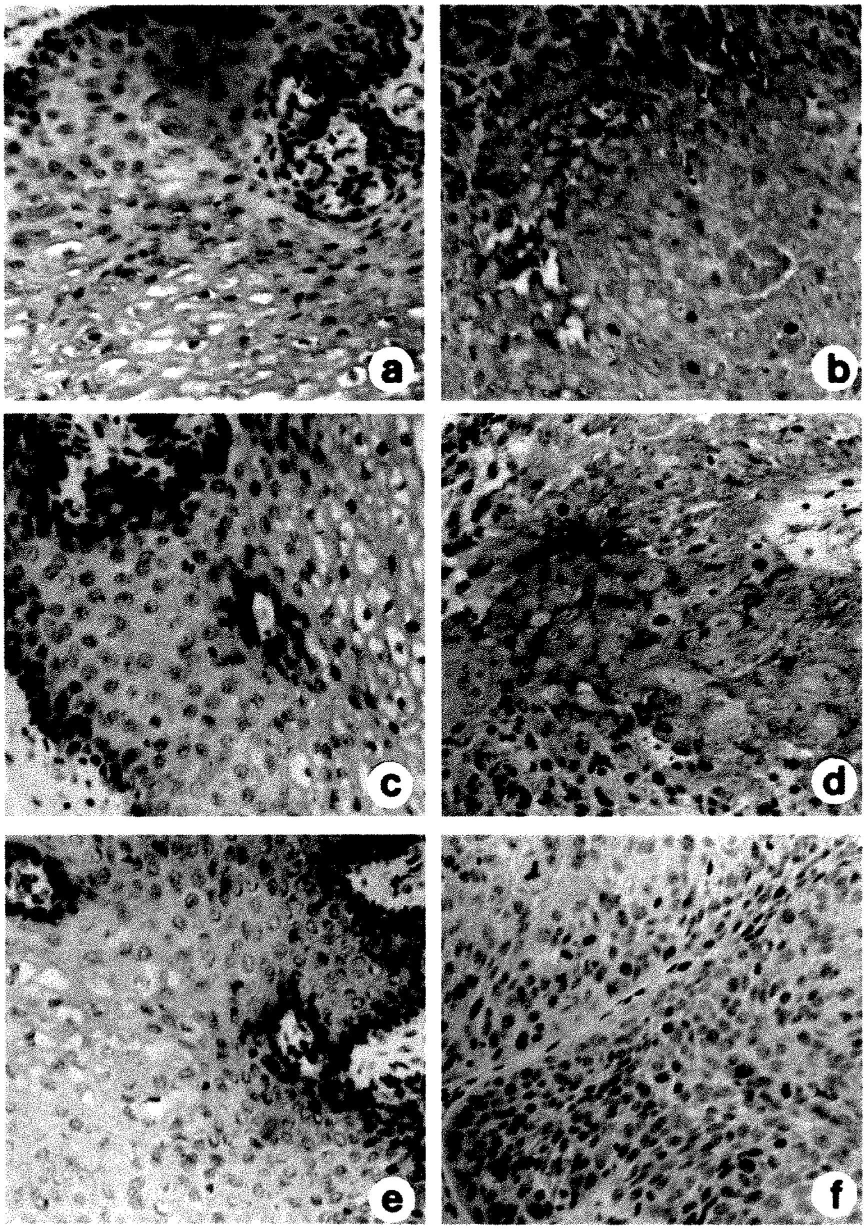


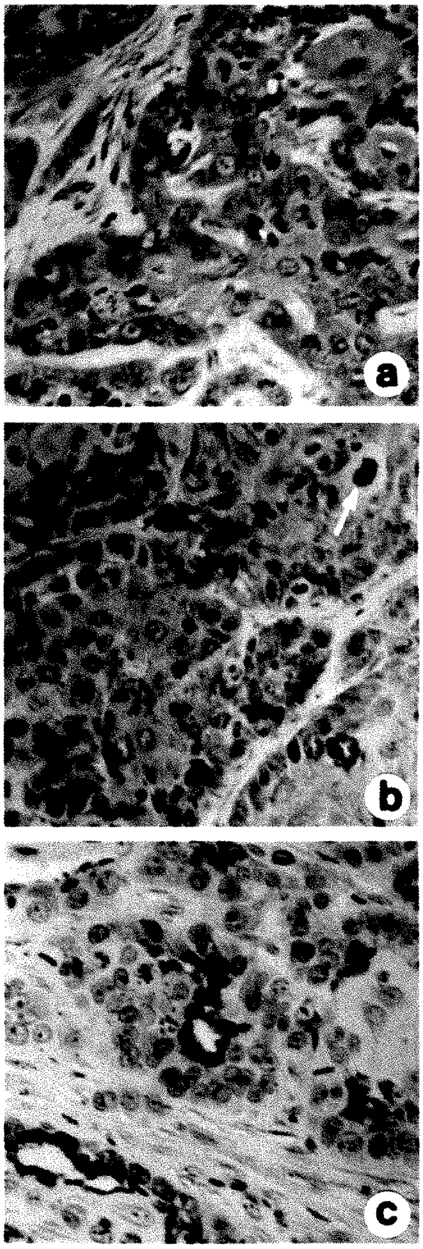
Fig 3.—Western blot of nude mouse tumor homogenate (042287AI). Lane A is stained with TuJ1, lane B with Tu9B, and lane C with no primary antibody. The same amount of protein was loaded in each lane.

Nine human squamous cell tumors grown in nude mice expressed the TuJ1 epitope, while one tumor did not (Table 2). Figure 3, a Western blot of a nude mouse tumor homogenate, illustrates positive staining for both the general β-tubulin antibody Tu9B (Fig 3A) and the TuJ1 antibody (Fig 3B). Immunocytochemistry was performed on paraffin sections made from three different nude mouse tumors that gave similar results. Color Fig 2 shows the results from one of these tumors. Sections of the nude mouse tumors exhibited staining with both the Tu9B general β-tubulin antibody (Color Fig 2, a) and with the TuJ1-specific β-tubulin antibody (Color Fig 2, b). A negative control demonstrated very little background staining (Color Fig 2, c). The arrow in Color Fig 2, b, indicates a mitotic cell stained with the TuJ1 antibody. Three tumors were examined by immunocytochemistry and all were positive for both the TuJ1 antibody and the general β-tubulin antibody Tu9B.

The results of experiments using cultured SCC cell lines were consistent with the results from the solid tissues. Figure 4 shows the Western blot results for three cultured cell lines (UM SCC 17B, UM SCC 17A, and UM SCC 38). All of these cell lines expressed



Color Fig 1.—Immunoperoxidase staining of normal oral epithelium (a, c, and e) and squamous cell carcinoma tumor tissue (b, d, and f). Tu9B antibody staining (a and b), TuJ1 antibody staining (c and d), and control staining (e and f) are shown (magnification, ×480).



Color Fig 2.—Immunoperoxidase staining of a squamous cell carcinoma tumor grown in a nude mouse (073086AI). Tu9B staining is shown in a, TuJ1 in b, and negative control staining in c. A mitotic cell, labeled with TuJ1, is shown by the arrow in b (magnification, ×400).

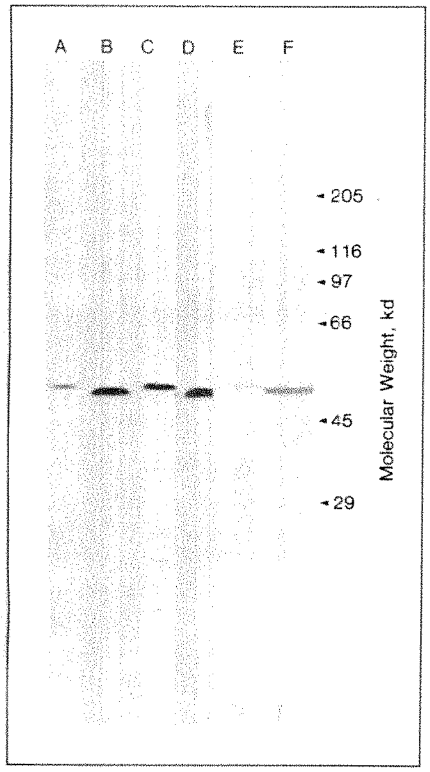


Fig 4.—Western blot of squamous cell carcinoma cell lines. UM SCC 17B (lanes A and B), UM SCC 17A (lanes C and D), and UM SCC 38 (lanes E and F) are shown. Lanes A, C, and E are stained with the TuJ1 antibody. Lanes B, D, and F are stained with the Tu9B antibody.

both the general β-tubulin antibody Tu9B (Fig 4, B, D, and F) and the TuJ1 antibody (Fig 4, A, C, and E). Figure 5 shows immunofluorescent microscopic results for each of these three cell lines, stained with Tu27 and TuJ1 antibodies followed by Texas Red-labeled secondary antibodies. Each cell line expressed positive microtubular staining for both the general β-tubulin monoclonal antibody (Tu27) (Fig 5, a, d, and g) and the TuJ1 monoclonal antibody (Fig 5, b, e, and h). All three cell lines expressed staining of both cytoplasmic microtubules and spindle microtubules. Secondary antibody controls were negative (Fig 5, c, f, and i).

The cell line UM SCC 17B was also stained with fluorescein-labeled secondary antibodies. One large cell exhibited an unusual staining pattern (Fig 6) with the TuJ1 antibody. In addition to the labeled microtubules, this cell exhibited brightly stained granules around the nucleus; it was the only cell observed to exhibit this pattern of staining.

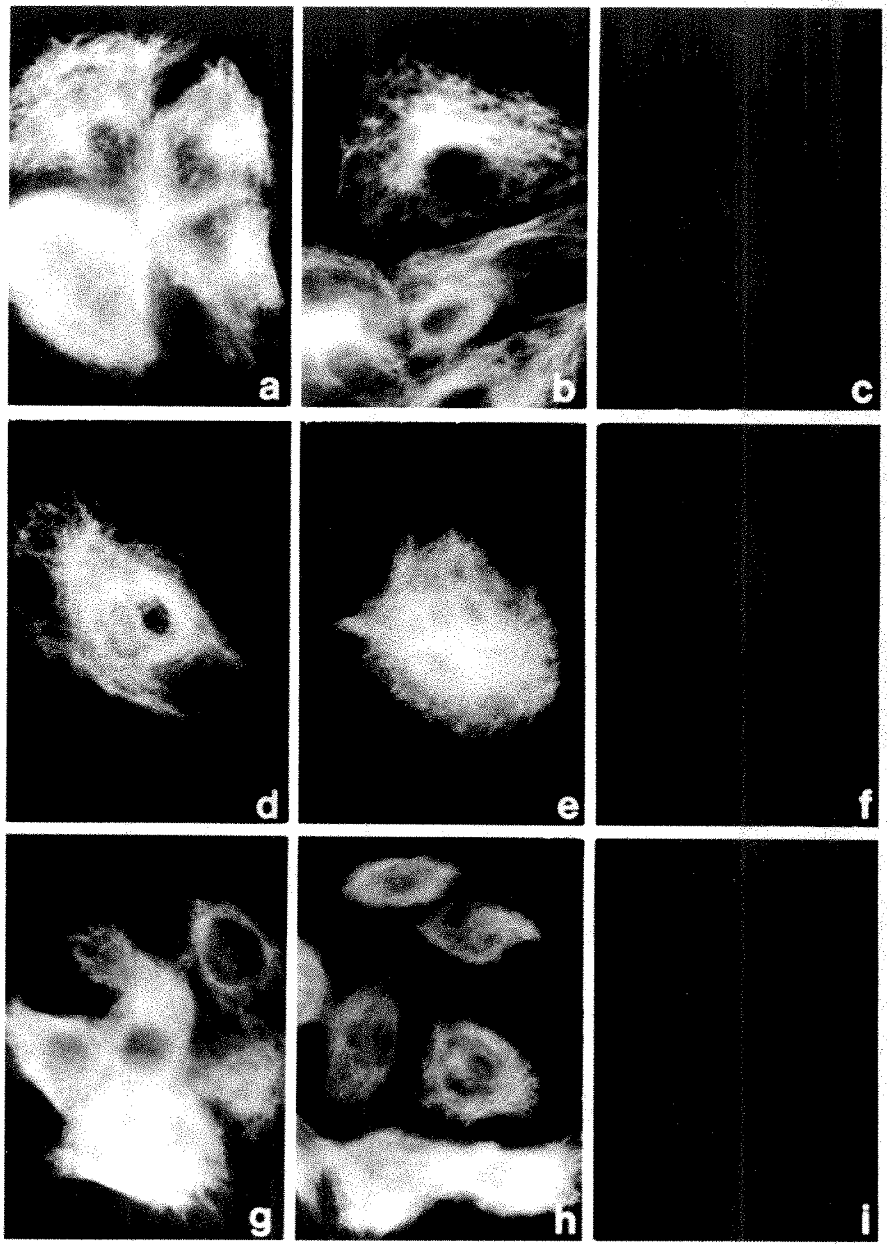


Fig 5.—Texas Red immunostaining of UM SCC 17B (a, b, and c), UM SCC 17A (d, e, and f), and UM SCC 38 (g, h, and i) cultured cell lines. The Tu9B antibody stains a, d, and g. The TuJ1 antibody stains b, e, and h. Nonspecific primary antibody stains c, f, and i (magnification: a through c, and g through i, ×1200; d through f, ×800).

COMMENT

Antibodies constitute one potentially useful class of probes for distinguishing normal from malignant cells. Most antibodies that have been reported to be tumor cell markers have recognized cell surface determinants,[29-32] and little attention has been paid to antibodies to cytoskeletal proteins as markers for transformed cells. Mammalian cells contain a number of different β-tubulin isotypes,[2,9,11,18] and antibodies made to β-tubulin can be isotype-specific or recognize epitopes common to all β-tubulins. We used two different types of β-tubulin monoclonal antibodies to characterize the staining of normal oral epithelial tissues and their malignant counterparts. Two monoclonal antibodies (designated Tu9B and Tu27) that stain all β-tubulin isotypes have been used. The third monoclonal antibody em-

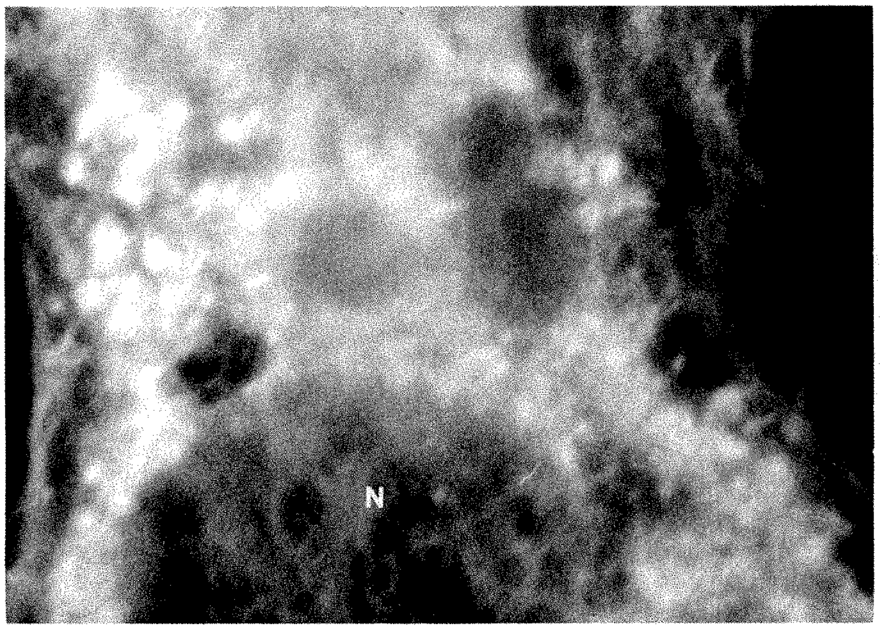


Fig 6.—Fluorescent immunostaining of UM SCC 17B stained with the TuJ1 antibody showing antibody-positive granules around the nucleus (N) (magnification, ×9600).

ployed in this study (designated TuJ1) is specific for a class-III β-tubulin isotype[15,21,22,33] that has been variously referred to as β′,[12,13,34] β_2,[18,35] β_3,[8] hβ4,[10] cβ4,[10,11] and Mβ6.[36,37]

This isotype of β-tubulin is generally referred to as being neuron-specific, although it has been found in the testis[36,37] in mammals but in no other normal tissue. The TuJ1 β-tubulin mouse monoclonal antibody reacts with tubulin on Western blots and with microtubules in neuronal cells from a wide variety of neural tissues,[15,19,20,38] testis,[20] and certain tumor tissues of presumed neuroepithelial origin.[21,22,33].

This study demonstrates by a combination of techniques that SCCs express the class-III β-tubulin isotype and that the TuJ1 β-tubulin monoclonal antibody can be used as a specific marker for SCCs as opposed to the normal oral epithelial cells from which these tumors arise. Western blot analysis of extracts from SCCs taken from patients, human SCCs grown in nude mice, cultured lines derived from human SCC, and control human oral mucosa demonstrated that only the SCC cells reacted with the TuJ1 antibody. Both tumor and normal human tissue reacted with the Tu9B and Tu27 broad-spectrum β-tubulin antibodies. These results were confirmed by immunocytochemical staining of tissue sections through normal human oral mucosa, human SCCs taken from patients, and sections of human SCCs grown in nude mice. Tumor sections exhibited consistent staining with both the TuJ1 and the broad-specificity antibodies, while the normal oral mucosa tissue stained only with the broad-specificity antibodies.

Finally, cultured cell lines derived from human SCCs were also found to immunostain with the TuJ1 monoclonal antibody. Together, these observations provide strong evidence that epithelial cells from the oral mucosa express the class-III β-tubulin isotype recognized by the TuJ1 mouse monoclonal antibody only after transformation to the malignant state, and that the vast majority of SCCs express this antigen. This is the first report of a nonneuroepithelial tumor that expresses the class-III β-tubulin isotype.

Squamous cell carcinoma cells undergoing mitosis express TuJ1. This was not observed in the case of cerebellar desmoplastic medulloblastoma[21] or primitive neuroepithelium of spontaneous ovarian teratomas.[33] Developing trigeminal neurons did not appear to express TuJ1 until the last cell cycle.[15]

The bright granules around the nucleus in the fluorescein-labeled, TuJ1-stained cell line UM SCC 17B (Fig 6) may represent a storage form of tubulin subunits. Two other nonmicrotubular staining patterns of a class-III β-tubulin have been reported. One pattern was a "reticular-network" in PtK_2 cells,[39] and the other a unique spatial distribution as a nonfilamentous, granular pattern in pheochromocytoma cells.[40]

A number of other tumor tissues examined in this study expressed TuJ1. It was expected that the three esthesioneuroblastomas would label with TuJ1.

Esthesioneuroblastomas are derived from the olfactory nerve tissue, and the tumor cells often have neuron-like characteristics.[41] The labeling by TuJ1 of aggressive fibromatosis cells, lymphoma cells, and malignant melanoma cells was unexpected, although additional testing may show the expression of the TuJ1 epitope in many other neoplasms. The probable explanation for the expression of TuJ1 by malignant melanoma lies in the embryology of melanocytes, which are derived from the neural crest. One group of researchers[12] found the tubulin isotype they called β′ to be present in a malignant melanoma cell line. This β′ can be traced to being a class-III β-tubulin.[11,18,34] The positive expression of TuJ1 by the lymphomas is not as easily explained. A patient was described with a B-cell lymphoma and autoantibodies to tubulin, although no specific isotype was determined.[42]

One of the biochemical changes that takes place during the differentiation of neurons is the expression of a class-III minor brain β-tubulin isotype recognized by the TuJ1 antibody.[8,13,15,38] This tubulin isotype is expressed, once the cells are committed to becoming neurons, about the time neurite outgrowth appears.[15] Mouse neuroblastoma cell lines (NIE 115, 18, Ns20, and N115) and multipotential embryonal carcinoma cell lines (1003 and 1009), induced to differentiate neurally, express this β-tubulin isotype.[8,12,34] The expression of this isotype occurs when the cells are committed to neural differentiation, even if neurite outgrowth is prevented.[12] In the neuroblastoma cell lines N115 and NIE 115, this tubulin isotype is posttranslationally modified by phosphorylation during neurite outgrowth.[8,34]

At this time, the class-III β-tubulin is the only β-tubulin isotype shown to be posttranslationally phosphorylated.[10] It is generally accepted that phosphorylation of the β-tubulin occurs on serine in vivo[8] Phosphorylation of tyrosine on β-tubulin in vitro by the $pp60^{src}$ gene product has been observed,[43] and the class-III β-tubulin is the only β-tubulin isotype with tyrosine in its unique carboxy-terminal amino acid sequence.[10,11,36,37]

It is far from clear what common features of cellular biochemistry or gene regulation result in the expression of the TuJ1 epitope in normal neurons, neuroblastomas, testis, malignant epithelial cells such as SCCs, and certain other apparently nonneuronal tumor sources. Nevertheless, the data presented in this article, coupled with the absence of expression of the TuJ1 β-tubulin epitope from most normal epithelial tissues of nonneuroectodermal origin, provide the opportunity to use this epitope as a marker for malignant transformation, at least in the case of SCC.

This study was supported by the University of Virginia Biomedical Research Support Grant, the Thomas F. and Grace D. Riggs Head and Neck Research Fund, National Institutes of Health grant GM28766, American Cancer Grant CD 344, and the John P. Edmondson Cancer Fund.

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The Efficacy of Cefaclor vs Amoxicillin on Recovery After Tonsillectomy in Children

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• Tonsillectomy and adenoidectomy continues to be one of the most commonly performed operations in the pediatric age group. The morbidity from tonsillectomy can be severe and includes throat and ear pain, fever, lethargy, and poor oral intake. A previous study at the Children's Hospital of Philadelphia (Pa) demonstrated the efficacy of amoxicillin therapy in minimizing some of these postoperative symptoms. However, some children continue to have a prolonged recovery even while receiving this antibiotic regimen. Because of these children and the high incidence of *Staphylococcus* found in tonsillar core tissue, a randomized, prospective study was undertaken at the Children's Hospital of Philadelphia to evaluate the efficacy of cefaclor vs amoxicillin in patients recovering from tonsillectomy. The patients received either ampicillin or cefazolin intravenously at the time of surgery and for 12 to 24 hours postoperatively. When oral intake was adequate, they received either amoxicillin or cefaclor orally for 7 additional postoperative days. Intraoperative cultures of the oropharynx and tonsillar tissue were obtained, as well as cultures of the tonsillar fossa 7 to 14 days postoperatively. The patients were evaluated for severity and duration of postoperative symptoms as well as complications. The results of this study showed no difference between the two groups of patients. We conclude that there is no justification for routine use of cefaclor over amoxicillin in the posttonsillectomy patient.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:590-593)

Tonsillectomy and adenoidectomy continues to be one of the most commonly performed operations, especially in the pediatric age group. The morbidity following tonsillectomy can be severe and includes throat and ear pain, fever, lethargy, and poor oral intake. A previous study at the Children's Hospital of Philadelphia (Pa) demonstrated the efficacy of antibiotic therapy in minimizing some of these postoperative symptoms.[1] However, clinical experience has shown that some patients have a protracted postoperative course even while receiving amoxicillin. Our own experience has shown improvement in those patients when treated with cefaclor. This finding, as well as recent studies[2-5] that have revealed an increasing percentage of *Haemophilus influenzae* and *Staphylococcus* species resistant to amoxicillin, prompted our investigation into other antibiotic agents for use in the posttonsillectomy patient. Cefaclor, because of its broad antibacterial spectrum as well as its low rate of side effects, was chosen for comparison with amoxicillin. We undertook to test the hypothesis that cefaclor would be more efficacious than amoxicillin in reducing postoperative morbidity in patients undergoing tonsillectomy and adenoidectomy.

PATIENTS AND METHODS

Each patient was evaluated by the attending otolaryngologist and entered into the study if he or she (1) was to undergo tonsillectomy with or without adenoidectomy; (2) had no known allergy to either cefaclor or amoxicillin; (3) had no medical condition that would require antibiotic therapy in the perioperative period, eg, bacterial endocarditis prophylaxis for cardiac anomalies; and (4) had not received antibiotic therapy in the week prior to tonsillectomy.

One hundred four children were entered into the study after informed consent was obtained. The protocol and consent forms were approved by the Committee for Pro-

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tection of Human Subjects of the Children's Hospital of Philadelphia.

Table 1.—Preoperative Profile

	Cefaclor Group	Amoxicillin Group
Average age, y	5.6	6.6
Sex, % M/F	42/58	42/58
Average No. of infections in last 12 months	2.9	2.7
History of airway obstruction during sleep, %		
Mild	4	7
Moderate	26	16
Severe	70	77
Preoperative tonsil size, % of patients		
2+	26	23
3+	61	62
4+	14	13
History of mouth breathing, %	96	95
Tonsillar erythema, %	52	44
Tonsillar crypt debris, %	10	9

Table 2.—Bacteriology Profile

	No. (%) of Patients*					
	Oropharynx		Tonsil Core		Postoperative	
	C	A	C	A	C	A
Normal respiratory flora	34 (65)	24 (56)	22 (42)	24 (56)	52 (100)	36 (84)
Coagulase-positive *Staphylococcus*	10 (19)	10 (23)	19 (37)	9 (21)	. . .	4 (9)
Group-A β-hemolytic *Streptococcus*	3 (6)	5 (12)	3 (6)	4 (9)	. . .	1 (2)
Haemophilus influenzae	5 (10)	4 (9)	7 (13)	5 (12)	. . .	1 (2)
Gram-negative microorganisms	. . .	. . .	1 (2)	. . .	. . .	1 (2)
Enterococcus	. . .	. . .	. . .	1 (2)	. . .	. . .

*C indicates cefaclor (n = 52); A, amoxicillin (n = 43).

Table 3.—Posttreatment Profile

	Cefaclor Group	Amoxicillin Group
Trismus, % of patients	29	37
Eschar, % of patients	75	81
History of bleeding postoperatively, % of patients	2	0
Nasal discharge, % of patients	17	16
Average % of body weight loss	4.5	3.8
Compliance, % of medication taken	88	89

The preoperative evaluation consisted of obtaining information on the patient's age, sex, weight, number of episodes of tonsillitis in the previous 12 months, and severity of obstructive symptoms during sleep. The presence or absence of mouth breathing and any associated medical problems were noted. Examination of the oropharynx revealed information on tonsillar size, erythema, and presence or absence of cryptic debris. The primary indication for the operation was also noted.

The children were prospectively randomized by the pharmacy to receive either cefazolin/cefaclor or ampicillin/amoxicillin perioperatively. After general anesthesia was induced, a culture swab of the oropharynx was obtained. The operation was then begun with an adenoidectomy performed initially, if indicated, followed by tonsillectomy. After the first tonsil was removed, the study medication was given intravenously. The tonsil was dipped in povidone-iodine (Betadine) for 30 seconds, rinsed in sterile saline solution, and sectioned, and a core sample was sent for microbiologic analysis.

Antibiotic dosages were simplified so that patients weighing 20 kg or more received 1 g of either ampicillin or cefazolin at surgery. Patients weighing less than 20 kg received 500 mg of either ampicillin or cefazolin at surgery. Equivalent doses of study medication were administered at 6-hour intervals in the short stay unit until discharge from the hospital. When the child was discharged, a bottle of study medication was given to the family. In children weighing 20 kg or greater, this consisted of either cefaclor or amoxicillin administered in doses of 250 mg three times daily for 7 days. In children weighing less than 20 kg, 125 mg of cefaclor or amoxicillin was administered three times daily for 7 days. Each family was given a checklist on which the parents were asked to record the child's temperature twice a day and to give subjective evaluations of the child's symptoms for the first 7 days postoperatively. These parameters included mouth odor, oral intake, pain, and level of activity. The administration of acetaminophen was permitted for analgesic and antipyretic effects.

A postoperative appointment was scheduled for 7 to 14 days following surgery. The child was examined and evaluated for the presence of trismus and eschar of the tonsillar fossa. A history of bleeding and significant nasal discharge was obtained from the parents. The child was weighed at this time and compliance with the study medication was determined as evidenced by the amount of medication remaining in the bottle. A swab of the oropharynx was obtained at this time for microbiologic analysis. Removal of patients from the study was left to the discretion of the attending otolaryngologist.

Once the data were collected from all study patients, the two groups were compared and the effects of cefaclor vs ampicillin were analyzed. The groups were compared on the following bases: (1) low-grade fever (number of times body temperature was measured at $\geq 37.8°C$ orally or its equivalent); (2) high fever (number of times body temperature was measured at $\geq 38.6°C$ orally or its equivalent); (3) percentage change in body weight; (4) subjective assessment of mouth odor (severe, moderate, or none); (5) amount of oral intake (measured as the number of days until the patient resumed eating soft foods or the usual diet; (6) level of pain (severe, moderate, mild, or none); and (7) activity level (measured as the number of days until the child resumed normal activities).

Techniques of microbial analysis of swabs from the oral cavity and core tonsillar tissue have been described in a previous report.[1]

RESULTS

Before completing the study, 9 patients were removed. One patient developed an erythematous rash in the perioral area 4 hours after receiving intravenous antibiotics. One patient in the cefaclor group had a significant episode of bleeding requiring surgical intervention and was excluded. Seven patients did not return for their follow-up visits and were, therefore, excluded. This left a study group of 95 patients.

Pretreatment Factors

Of the 95 patients completing the study, 52 received cefazolin/cefaclor therapy and 43 received ampicillin/amoxicillin therapy. The average age in the cefaclor group was 5.6 years, and in the amoxicillin group, 6.6 years. Approximately 42% of the subjects in each group were male. There were no statistically significant differences between the two groups with respect to the average number of infections in the previous 12 months, history of airway obstruction during sleep, history of mouth breathing during the day, tonsil size, tonsillar erythema, and/or tonsillar cryptic debris (Table 1). Preoperative bacteriologic evaluation revealed similar flora between the two groups, with normal respiratory flora composing 66% of the oropharyngeal cultures in the cefaclor group and 56% in the amoxicillin group (Table 2). No anaerobic organisms were isolated preoperatively.

Posttreatment Factors

Overall compliance with the study was good, with 88% of the medication used in the cefaclor group and 89% in the amoxicillin group. No statistically significant differences were seen between the two groups when compared for the presence of trismus, eschar, nasal discharge, percent of body weight loss, or significant episodes of bleeding (Table 3).

No statistically significant differences could be demonstrated between the groups when the factors of fever, odor from the oral cavity, oral intake, pain, and activity level were examined.

Low-grade fever is common after tonsillectomy and the use of cefaclor did not seem to alter this phenomenon. There were 1.6 observations of fever to 37.8°C or higher in the cefaclor group vs 1.3 observations in the amoxicillin group. High fever ($\geq$38.6°C), however, was not commonly seen, with an average of less than one observation (0.1) made in the cefaclor group vs none in the amoxicillin group.

Offensive mouth odor is also commonly noted in this postoperative population, with 2.4 days of moderate mouth odor and 0.6 days of severe mouth odor noted in the cefaclor group. This compared with 2.5 days of moderate mouth odor and 0.7 days of severe mouth odor noted in the amoxicillin group.

Pain was subjectively recorded by the parents as mild, moderate, or severe. Those in the cefaclor group experienced an average of 3.9 days of mild, moderate, or severe pain, vs 3.8 days in the amoxicillin group.

Most children returned to a soft or normal diet fairly quickly: 4.2 days in the cefaclor group vs 4.3 days in the amoxicillin group.

The children returned slowly to their normal activities: 5.1 days until normal activity was noted in the cefaclor group vs 4.9 days in the amoxicillin group.

Postoperative Bacteriology

Although cefaclor possesses a broader range of antimicrobial activity, this did not appear to play a significant part in our postoperative culture results (Table 2). All of the postoperative cultures in the cefaclor group revealed normal respiratory flora, vs 84% in the amoxicillin group. There were four cases of coagulase-positive *Staphylococcus* in the amoxicillin group (9%), as well as one case each of group-A β-hemolytic *Streptococcus*, *H influenzae*, and a gram-negative organism (each 2% of the total) in the amoxicillin group.

COMMENT

Tonsillectomy (with or without adenoidectomy) continues to be one of the most commonly performed operations in the pediatric age group. Morbidity from this procedure can be protracted and includes foul mouth odor, oral pain, lethargy, weight loss, and poor oral intake. A previous study by Telian et al[1] showed the superiority of antibiotics (amoxicillin) over placebo in reducing several factors of postoperative morbidity. These included a lower incidence and shorter duration of fever, as well as an earlier return to usual diet and activities. A shorter duration of pain and a shorter duration and reduced severity of mouth odor was also noted in the antibiotic-treated group. Since the publication of that article, it has become the routine practice at several institutions to use antibiotics in treating children after tonsillectomy and/or adenoidectomy.

While most patients do well on this regimen, some children still demonstrate a protracted recovery after tonsillectomy. These children are usually switched to cefaclor, and it has been our impression that the broader-spectrum antibiotic hastens recovery.

Recent bacteriologic data from our institution also help to support the impression that cefaclor might be more efficacious than amoxicillin in the management of patients after tonsillectomy. DeDio et al,[2] in their recent review of microbiology of the tonsils and adenoids, identified *Staphylococcus aureus* and *Haemophilus* species as the most frequent pathogens cultured in core tonsil and adenoid tissue. *Haemophilus* species were identified in 54% and *S aureus* in 46% of their patients. They report that only 8% of all *S aureus* isolates at the Children's Hospital of Philadelphia have been shown to be susceptible to penicillin G or amoxicillin by in vitro susceptibility testing. In addition, 17% to 20% of non-type-B *Haemophilus* species were noted by these authors to be producers of β-lactamase.

These findings, as well as our clinical experience with cefaclor, prompted our investigation into the efficacy of cefaclor compared with amoxicillin in the posttonsillectomy patient. Cefaclor is a semisynthetic cephalosporin for oral administration. It is well absorbed after oral administration to fasting subjects, which we felt was important in the posttonsillectomy population with poor oral intake. In vitro tests have demonstrated that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis.[6] Its spectrum of activity includes staphylococci, *Streptococcus pyogenes* species, *Streptococcus pneumoniae*, *Branhamella catarrhalis*, *H influenzae*, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* species.[6] Adverse reactions are described as gastrointestinal symptoms in 2.5% of patients, and hypersensitivity reactions (manifesting as a rash) in 1.5% of patients.[7] Cefaclor's broad spectrum of activity against β-lactamase-producing strains of *H influenzae* and *S aureus*, as well as the low incidence of hypersensitivity reactions, made it a logical choice for comparison with amoxicillin. We felt that extensive anaerobic coverage was not needed because of the paucity of anaerobes isolated in previous studies of microbial flora of the tonsils and adenoids at our institution, although other authors report incidences as high as 4.1 anaerobic organisms per tonsil in their studies.[4,5]

Posttreatment analysis of oropharyngeal cultures revealed the presence of *S aureus* in 9% of posttreatment cultures in the amoxicillin-treated group. The finding did not, however, appear to have a statistically significant effect on postoperative morbidity in our study. However, in those patients with poor clinical response to amoxicillin postoperatively, the possibility of organisms resistant to amoxicillin must be considered, as should the use of cefaclor or another broad-spectrum antibiotic.

CONCLUSION

The routine use of cefaclor in posttonsillectomy patients does not appear to be warranted. There are no statistically significant differences between cefaclor and amoxicillin when factors such as fever, pain, oral intake, weight loss, and activity level are compared. We continue to use antibiotics in the postoperative period because of the benefit shown in previous studies. However, amoxicillin should be used for routine postoperative treatment unless contraindicated. Cefaclor should be reserved for the child who (despite the standard amoxicillin treatment) demonstrates a protracted or difficult recovery after tonsillectomy.

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IN OTHER AMA JOURNALS

AJDC

Age-Related Patterns of Violent Death, Cook County, Illinois, 1977 Through 1982
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Fetal Surgery in the 1990s
Mark I. Evans, MD; Arie Drugan, MD; Frank A. Manning, MD; Michael R. Harrison, MD (*AJDC.* 1989;143:1431-1436)

Regulation of Oxygen Concentration Delivered to Infants Via Nasal Cannulas
Nestor E. Vain, MD; Luis M. Prudent, MD; Deborah P. Stevens, RRT; Margaret M. Weeter, RRT; M. Jeffrey Maisels, MB, BCh (*AJDC.* 1989;143:1458-1460)

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Nicola Principi, MD; Paola Marchisio, MD; Emilia Massironi, MD; Rosa Maria Grasso, MD; Gianfranco Filiberti, MD (*AJDC.* 1989;143:1414-1418)

Study of Virus Isolation From Pharyngeal Swabs in Children With Varicella
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Airway Complications in CHARGE Association

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• The association between catastrophic airway events and developmental delay was examined in patients with CHARGE (coloboma, heart disease, atresia choanae, retarded growth and/or development, genital hypoplasia, and ear anomalies and/or deafness) association. A retrospective chart analysis was performed from The Children's Hospital in Boston, Mass. Sixteen patients were identified with CHARGE association. Nine patients had at least one respiratory arrest, and 7 had no airway difficulties. Some degree of developmental delay was seen in 14 patients, but was most severe in those patients who suffered a respiratory arrest. We conclude that children with CHARGE association have a propensity for airway instability and that cerebral hypoxia contributed to the developmental delay in some of our patients. We recommend early tracheotomy rather than early choanal atresia repair in these patients to protect the central nervous system.

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The acronym *CHARGE,* coined by Pagon et al[1] in 1982, refers to a complex of malformations that includes *c*oloboma, *h*eart disease, *a*tresia choanae, *r*etarded growth and/or development, *g*enital hypoplasia, and *e*ar anomalies and/or deafness. The pathogenesis of the anatomic malformations is thought to be secondary to the abnormal development of the neural crest during embryogenesis. The etiology of the developmental delay remains unclear; some patients have obvious central nervous system defects, while others do not. The severity of mental retardation and/or developmental delay is not predictable.

We undertook a review of our patients with CHARGE association after we noted an inordinate number of airway complications in these patients. The purpose of this study was to review the number of airway complications in our patients with CHARGE association to see if these complications were associated with the severity of mental retardation and/or developmental delay.

SUBJECTS AND METHODS

A retrospective review of charts of patients with CHARGE association from The Children's Hospital Medical Center in Boston, Mass, was performed for the years 1980 through 1988. Data on the following factors was collected and tabulated; type of choanal atresia and number of repairs, degree of mental retardation, anatomic abnormalities of the central nervous system (CNS), number of clinically significant airway events defined as cardiorespiratory arrest or severe birth hypoxia, and whether a tracheotomy was performed.

RESULTS

Sixteen patients were identified with CHARGE association (Table): 1 had choanal stenosis and 15 had choanal atresia (13 bilateral and 2 unilateral). Eleven cases of choanal atresia were repaired; follow-up was longer than 3 months in 10 cases. Nasal airway patency was accomplished in 5 patients, 3 of whom required at least one revision. Five patients restenosed, 3 in spite of multiple revisions, and 2 required tracheotomy.

A total of 5 patients underwent tracheotomy. Two patients failed multiple attempts at choanal atresia repair; 1 had choanal stenosis but had several cardiorespiratory arrests; and 2 had no previous choanal atresia repair. Of these 2 patients, 1 had unilateral choanal atresia but had a cardiorespiratory arrest with resultant anoxic encephalopathy at age 10 months. The other had an absent corpus callosum and a severely deformed nasopharynx with multiple apneic episodes shortly after birth.

Nine patients had clinically significant obstructive airway events. Six of these patients developed severe mental retardation, 2 of whom died secondary to an obstructive upper airway event; 1 patient died 1 day postpartum of cardiorespiratory arrest; and 2 had mild to moderate developmental delay. Seven patients had no airway difficulties. Six of these patients had mild to moderate developmental delay; the other was too young to assess the degree of developmental problems.

Computed tomographic scans of the brain were performed in 12 cases. A congenital CNS anomaly was found in 3 patients, 2 had partial agenesis, and 1 had complete agenesis of the corpus callosum. One of these patients was severely retarded, but also suffered a cardiorespiratory arrest; the other 2 had only mild developmental delay.

COMMENT

Airway volatility as a part of CHARGE association has yet to be re-

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Summary of Patient Data

Patient No.	Tracheotomy	Type of Choanal Atresia	Degree of Mental Retardation	Airway Event
1	No	Bilateral	Mild	No
2	Yes	Unilateral	Severe	Yes
3	Yes	Bilateral	Mild	Yes
4	No	Bilateral	Severe*	Yes
5	No	Bilateral	Mild	No
6	No	Bilateral	Severe*	Yes
7	Yes	Bilateral	Mild	No
8	No	Bilateral	Severe	Yes
9	No	Bilateral	Died at age 1 d	Yes
10	No	Bilateral	Severe	Yes
11	No	Bilateral	Severe	Yes
12	No	Bilateral	Mild	No
13	No	Bilateral	. . .†	No
14	Yes	Bilateral	Mild	No
15	No	Bilateral	Mild	No
16	Yes	Choanal stenosis	Severe	Yes

*Died of obstructive airway event.

†Patient too young to assess degree of developmental delay.

ported. Airway complications developed in 9 (56%) of our 16 patients. The etiology of such a large number of airway problems remains speculative. Deformities of the airway are a likely possibility. Coniglio et al[2] evaluated the nasopharynx by computed tomographic scan in children with CHARGE association and found significant anatomic deformity. As well as having bilateral choanal atresia, the nasopharynx was contracted in the lateral and/or vertical dimension. In addition, there was an abnormally prominent bony medial pterygoid lamina and a thickened vomer and posterior nasal septum. Incoordination of the hypopharynx may be another cause of airway instability. Oley et al[3] described 5 patients with significant feeding difficulties and evidence of velopharyngeal incoordination and/or gastroesophageal reflux. One patient in our series who required a tracheotomy had documented reflux with recurrent aspiration pneumonia. All patients in our series appeared to have swallowing problems; their parents reported pooling of secretions, choking, and vomiting. The etiology of the swallowing problems in these children has not yet been determined but will be the subject of a future study. It appears that a combination of the anatomic and physiologic factors creates the potential for a catastrophic airway event to occur.

Successful repair of choanal atresia in the child with CHARGE association is more difficult than in an otherwise normal child. Coniglio et al[2] reported that 7 of 9 patients with CHARGE association required revision surgery, whereas only 1 of 15 non-CHARGE association children required surgical revision of the initial choanal atresia repair. They hypothesized that the high failure rate among babies with CHARGE association was secondary to the abnormal anatomy of the nasopharynx, which caused restenosis. In our series, 70% of our initial surgical repairs failed, which corroborates their finding.

Developmental delay, an important feature of CHARGE association, presents in various degrees. In some cases, CNS abnormalities may account for the mental retardation. In other cases, no CNS abnormalities are present. Pagon et al,[1] in their initial series of patients, reported in IQ score range of 70 to 80. Hall[4] reported a range of 30 to 70. Oley et al,[3] in their series of 20 patients, reported growth delay in 17 patients and mental retardation in 12, only 3 of whom were profoundly retarded. In our series, 15 of 16 patients had developmental delay, 7 of whom were severely retarded. Although the correlation between mental retardation and catastrophic airway events is only clinical, all of our patients with severe mental retardation had at least one cardiorespiratory arrest.

From our retrospective analysis it appears that children with CHARGE association have a propensity for airway instability. It also appears that early repair of bilateral choanal atresia in these children is rarely successful. Given that many of these children will only be mildly mentally retarded if they suffer no injury to their central nervous systems, we would like to propose that early tracheotomy be performed to protect the central nervous system from potential anoxic injury. Choanal atresia repair should be delayed until the child is at least 2 years old, when the operation is more likely to be a success.

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Editorial Footnote

Most of the literature dealing with choanal atresia has supported the general concept of early repair of the atresia and avoidance of tracheotomy. When the child is otherwise healthy, this approach has led to generally favorable outcomes.

The authors of this article present a special subgroup of patients in whom they propose tracheotomy rather than early choanal atresia repair. They base their recommendation on the observed volatility or instability of the airway in babies with the CHARGE association and the high rate of failure of the atresia repair.

Our reviewers were favorable in their assessment of this manuscript and they concur with publication of this work. It is noted, however, that other groups have not observed these same problems, and that this issue may not yet be completely resolved. Perhaps there will be some patients who should have choanal atresia repair accomplished earlier, and others in whom it should be postponed in preference to a tracheotomy. In any event, it is a valuable contribution to our understanding of the challenging problems of airway management in neonates with congenital airway disorders.

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Clinical Notes

Combined Median Mandibulotomy and Weber-Fergusson Maxillectomy

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• Monoblock surgical resection in combination with radiotherapy remains the most effective method of treatment for advanced carcinoma of the maxillary sinus. Extension of antral carcinoma into the infratemporal and pterygopalatine fossae decreases the probability of achieving an all-encompassing resection via the classic anterolateral Weber-Fergusson approach because of limited posterior access. Temporal and lateral infratemporal fossa approaches have been described and involve either mobilization of the zygomatic arch or a lateral mandibular osteotomy, respectively. We report the use of a median labiomandibulotomy combined with the Weber-Fergusson approach for lesions extending posteriorly. The labiomandibulotomy with paralingual extension along the floor of the mouth allows rotation of the coronoid process laterally and exposes the infratemporal fossa to its posterior margin. We present two cases in which this approach was used to extirpate lesions that had extended posteriorly. Relevant anatomy, operative technique, potential complications, and limitations, as well as a comparison with other methods of exposure, are discussed.

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Posterior extension of antral malignancy into the infratemporal and pterygopalatine fossae decreases the likelihood of achieving an all-encompassing resection by the standard anterolateral Weber-Fergusson maxillectomy because of limited posterior access. Attempts at inclusion of the pterygoid plates, pterygoid musculature, and infratemporal fossa contents via an anterolateral approach are hampered by poor visibility due to bleeding from the pterygoid venous plexus and the internal maxillary artery. Furthermore, the creation of the posterior osteotomy is difficult without direct access into the infratemporal fossa and compromises the critical posterior resection margin, as well as endangering vital adjacent structures such as the internal carotid artery and the floor of the middle cranial fossa. The purpose of this article is to report the use of a combined median labiomandibulotomy-Weber-Fergusson approach for resection of antral malignancies with posterior extension. Section of the mandible in the midline with paralingual extension by division of the soft tissues of the floor of the mouth allows rotation of the mandible with its coronoid process laterally, exposing the infratemporal fossa to its posterior margin. This improved surgical access permits controlled monoblock resection of such advanced maxillary tumors.

TECHNIQUE

The method of maxillectomy described includes resection of the orbital floor with preservation of the orbital contents, but can readily be modified to include orbital exenteration.

After the induction of general endotracheal anesthesia, tarsorrhaphy sutures of 5-0 silk are placed to protect the eyes. A standard Weber-Fergusson skin incision is performed (Fig 1). This involves division of the upper lip through the philtrum in a staggered fashion, to prevent contracture and to provide scar camouflage. The superior labial artery is ligated. The incision is continued around the alar margin along the nasofacial sulcus to the medial canthal region and then carried laterally along the lower eyelid. Extension to the lateral canthal region provides access to the superolateral maxilla. The mucosa of the maxillary gingivobuccal sulcus is incised backward from the point where the lip-splitting incision was made beyond the maxillary tuberosity. The cheek flap is elevated and rotated laterally in a supraperiosteal plane, exposing the nasal bone medially, the infraorbital rim superiorly, and the zygoma and the outer aspect of the maxilla laterally (Fig 2). The infraorbital neurovascular bundle is divided and ligated. The integrity of the anterolateral maxillary wall is evaluated as the flap is elevated so that a cuff of normal soft tissue is left on the anterior aspect of the specimen. The medial aspect of the orbit is now explored by detaching the medial canthal ligament and elevating the periosteum laterally. The anterior and posterior ethmoidal arteries are ligated, the lacrimal sac is transected and marsupialized, and the orbital contents are displaced laterally. The orbital floor is then explored by raising the periosteum. If no evidence of tumor invasion exists medially or inferiorly, the maxillectomy can proceed with preservation of the orbital contents.

The technique of median labiomandibulotomy is performed as previously described by Biller et al.[1,2] The lower lip is split in the midline in a staggered fashion from the vermilion border to the submental skin crease. The incision is extended horizontally backward over the hyoid bone and sternocleidomastoid muscle and then is carried superiorly toward the mastoid process (Fig 1). The full thickness of the lower lip is divided, and the inferior labial artery is ligated. The neck incision is carried through the platysma to the deep cervical fascia. Care is taken to avoid injury to the mandibular branch of the facial nerve. The periosteum of the mandibular symphysis is elevated bilaterally for a distance of 2 to 3 cm. The mandibular osteotomy is outlined from a point between the central incisor teeth downward in a staircase fashion to the inferior border of the mandible adjacent to the midline. Two pairs of bur holes are drilled on either side of the projected bone cut to facilitate later transosseus wiring for fixation. A Gigli saw is introduced between the central incisor teeth for division of the mandible. Care is taken to bevel both the vertical and horizontal limbs of the osteotomy to ensure stable reapproximation of the mandible. The mucosa of the

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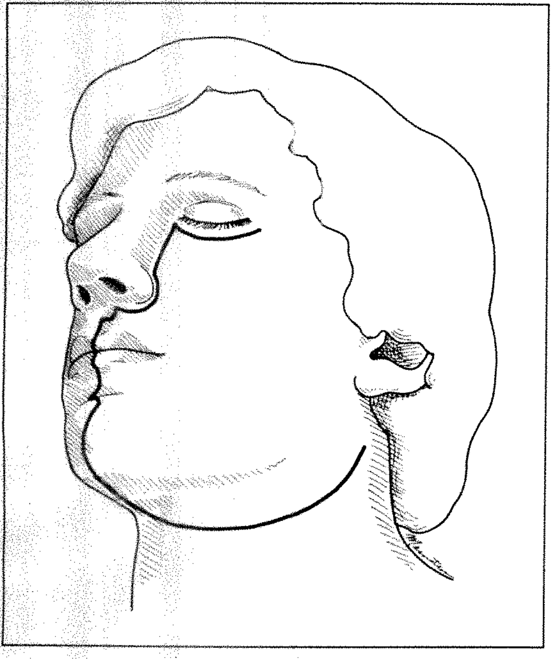

Fig 1.—Skin incisions outlined for a combined median labiomandibulotomy-Weber-Fergusson approach.

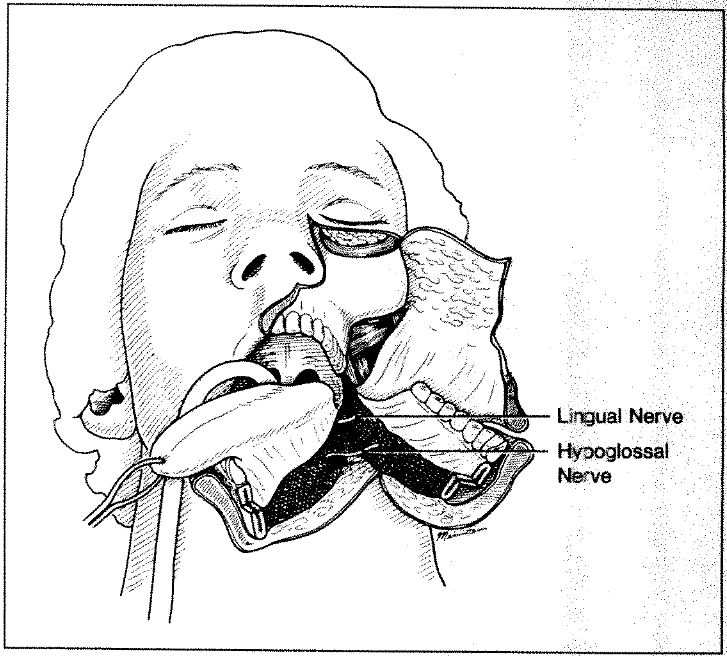

Fig 2.—The cheek flap has been elevated, exposing the maxilla. The median labiomandibulotomy with a paralingual extension has been completed, preserving the lingual and hypoglossal nerves. Detachment of the pterygoid muscles will now provide direct access into the infratemporal fossa.

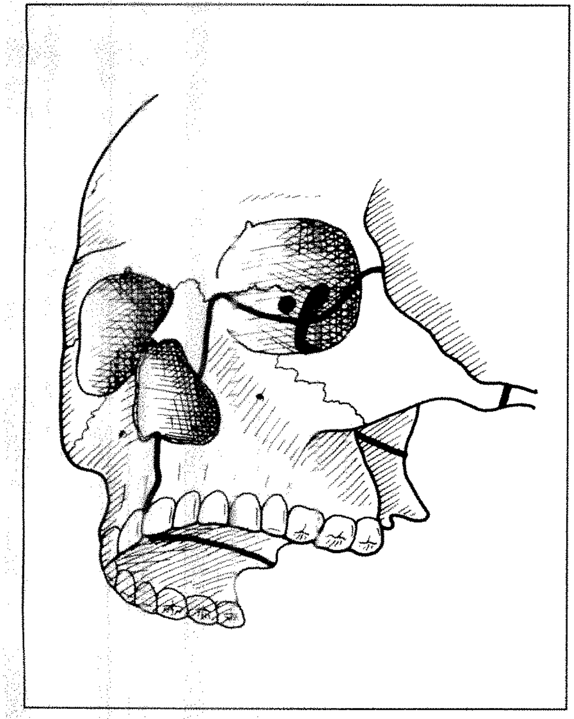

Fig 3.—The osteotomies for maxillectomy are outlined.

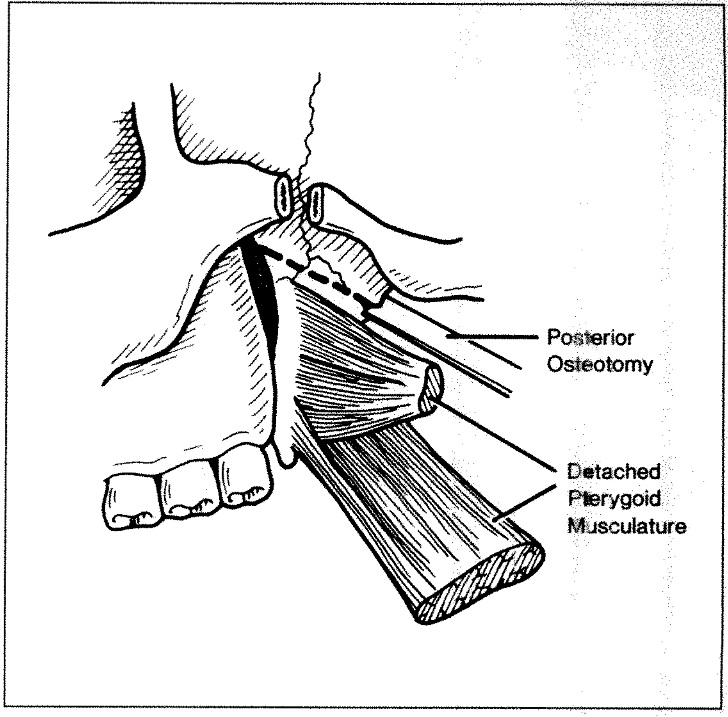

Fig 4.—The posterior osteotomy is made transversely through the base of the pterygoid plates and extends into the pterygopalatine fossa and inferior orbital fissure.

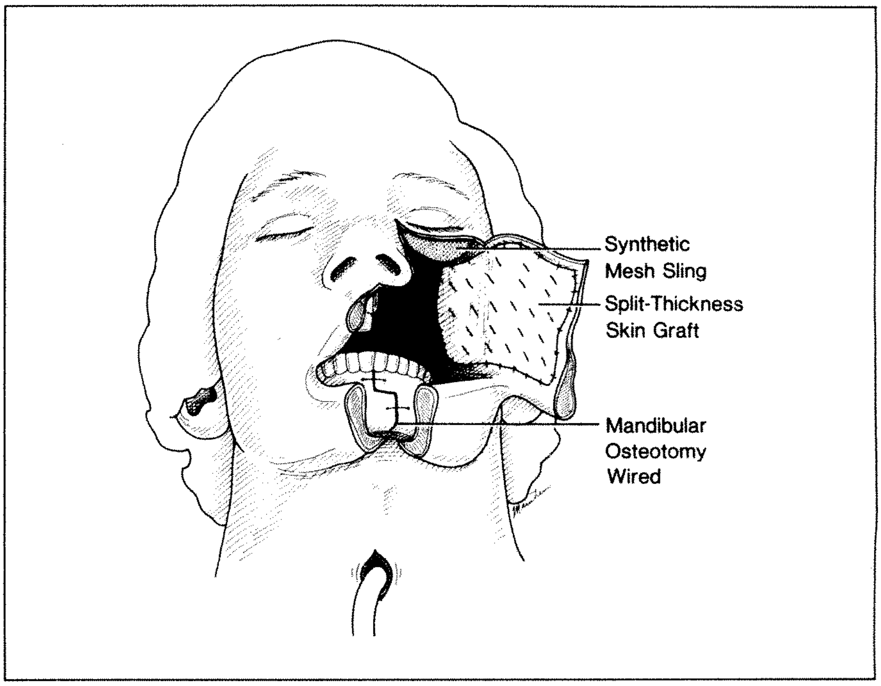

Fig 5.—Reconstruction involves suspension of the orbital contents with a synthetic (Marlex) mesh sling, a split-thickness skin graft sutured to the check flap, closure of the mandibular osteotomy, and placement of a palatal obturator (not shown).

floor of the mouth is incised between the orifices of the submandibular duct. The incision is carried posteriorly along the floor of the mouth, then laterally to the anterior tonsillar pillar, and then superiorly to join the incision in the maxillary vestibule (Fig 2). Blunt dissection with a clamp helps to identify the lingual and hypoglossal nerves. Division of the submandibular ganglion and the submandibular duct facilitates lateral rotation of the mandible with preservation of the lingual and hypoglossal nerves. Lateral displacement of the mandible produces rotation of the coronoid process and provides access into the infratemporal fossa (Fig 2).

An osteotomy is performed along the frontonasal process of the maxilla. A medial orbital osteotomy is then made below the frontoethmoidal suture line, which extends laterally and downward into the inferior orbital fissure. Th zygomatic arch is sectioned (Fig 3). An angled clamp is used to pass a Gigli saw from the inferior orbital fissure into the infratemporal fossa, and the lateral wall of the orbit (frontal process of the malar bone) is divided. The upper incisor tooth on the side of the resection is removed. A stab incision is made into the nasal cavity at the posterior edge of the hard palate. A curved clamp is inserted along the floor of the nasal cavity into this incision while the end of the Gigli saw, which is used to transect the hard palate, is grasped. An incision is then carried across the posterior aspect of the hard palate, separating it from the soft palate. All that now remains is the posterolateral attachment and the infratemporal fossa contents. An attempt is made to identify and ligate the internal maxillary artery. The pterygoid muscles are detached from their insertions. The posterior osteotomy is made transversely along the base of the pterygoid plates and extends into the pterygopalatine fossa and inferior orbital fissure (Fig 4). The contents of the infratemporal and pterygopalatine fossae are included in the specimen. The remaining soft-tissue attachments are readily transected with a scissors, and the specimen is delivered en bloc. The margins of resections are carefully inspected for tumor, and frozen sections are sent from any questionable area.

The orbital floor is reconstructed with synthetic (Marlex) mesh suspended between the medial and lateral orbital walls (Fig 5). It is placed below the periosteum, which was previously elevated and preserved with the orbital contents. A split-thickness skin graft is sutured to the buccal mucosa and covers the intraoral aspect of the cheek flap to diminish crusting and granulation tissue and to reduce contracture. A preoperatively prepared palatal prosthesis is placed to allow early resumption of oral feeding and to permit normal speech. The cavity is packed with antibiotic-impregnated gauze, and the cheek flap is closed in two layers. The mucosa of the floor of the mouth is closed, and the suprahyoid musculature is reapproximated. Transosseus wires are placed across the mandibular osteotomy site and tightened. The lip is closed in layers, taking care to realign the vermilion border accurately. The platysma is reapproximated and the cervical skin incision is then closed. A Penrose drain is placed. A tracheostomy is routinely performed, and a nasogastric tube is inserted.

REPORT OF CASES

Case 1.—A 70-year-old Hispanic man presented which chronic right-sided maxillary sinusitus. Sinus roentgenograms demonstrated opacification of the right maxillary sinus but no evidence of bone erosion. An intranasal antrostomy and a mucosal biopsy were performed and revealed squamous cell carcinoma. A computed tomographic scan of the paranasal sinuses demonstrated a lesion within the right maxillary sinus extending posteriorly into the infratemporal and pterygopalatine fossae and involving the pterygoid musculature (Fig 6). There was no evidence of skull base erosion or intracranial extension. The patient received 55 Gy of preoperative radiotherapy followed by a combined median labiomandibulotomy-Weber-Fergusson approach for resection of the lesion. Frozen sections were negative for tumor. The patient's postoperative course was uneventful. He underwent decannulation on the 10th day and resumed oral feedings on the 14th day. Persistent right lower-eyelid edema present at the time of discharge gradually subsided. A follow-up computed tomographic scan 6 months postoperatively revealed no evidence of disease (Fig 7).

Case 2.—A 29-year-old white man presented with a recurrent chondrosarcoma of the maxillary sinus 4 years after undergoing a maxillectomy with orbital exenteration. The recurrence involved the infratemporal fossa and parapharyngeal space. A combined median mandibulotomy-Weber-Fergusson approach was utilized to extirpate the lesion. The surgical specimen included the pterygoid plates and the pterygoid musculature. Margins were negative for tumor. The patient was free of disease on follow-up examination 3 years postoperatively.

COMMENT

The combined median labiomandibulotomy-Weber-Fergusson approach is applicable to maxillary tumors showing evidence of posterior extension. This may involve bony destruction of the posterior sinus wall and the

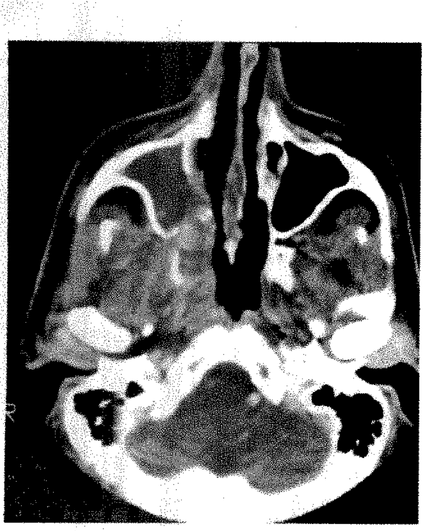

Fig 6.—Computed tomographic scan demonstrating posterior extension of antral carcinoma into the infratemporal and pterygopalatine fossae with involvement of the pterygoid musculature.

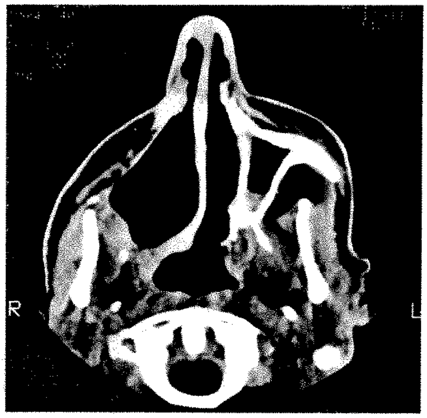

Fig 7.—Computed tomographic scan obtained after a combined median mandibulotomy-Weber-Fergusson maxillectomy. Note complete maxillectomy with absence of the pterygoid plates.

pterygoid plates or frank invasion into the infratemporal and pterygopalantine fossae with involvement of the pterygoid musculature. The labiomandibulotomy can be extended to gain simultaneous control of the great vessels in the neck and exposure of the medial and lateral compartments of the skull base.[1,2]

Contraindications for this procedure include erosion of the skull base, evidence of intracranial extension, unresectable regional metastases, and distant metastases. Tumor in the pterygopalatine fossa may extend intracranially through the foramen rotundum to involve the gasserian ganglion. In patients with midfacial pain and paresthesias, trigeminal nerve root involvement must be ruled out, preoperatively. Selected cases with anterior skull base involvement or intracranial extension may be managed with combined craniofacial resection.[3]

The potential complications of the procedure are primarily those associated with maxillectomy and mandibulotomy. Hemorrhage may result from inadequate control of the internal maxillary artery or its branches, the anterior or posterior ethmoidal arteries, and the pterygoid venous plexus. Retraction on the globe and dissection in the region of the orbital apex place the optic nerve at risk. Prolonged lower-eyelid edema may occur, as noted in our first patient, secondary to interruption of the lymphatic and venous drainage during elevation of the flap. Ptosis, enophthalmos, diplopia, and epiphora may also occur. Extrusion of the synthetic mesh sling supporting the orbital contents has been reported. Cerebrospinal fluid leak from inadvertent entrance into the cranium may result if the surgical resection margin is not kept below the frontoethmoidal suture line. Skin graft slough, flap contracture, and necrosis have also been reported. Complications associated with the mandibulotomy are few; however, orocutaneous fistulas and nonunion of the osteotomy have been reported. The median mandibulotomy necessitates the performance of a tracheostomy for protection of the airway.

Alternative methods for exposure of the retromaxillary-infratemporal region exist. A lateral approach described by Dingman and Conley[4] utilizes a lower-lip-splitting incision with a lateral mandibular osteotomy or an ostectomy to provide direct access to the infratemporal fossa. The midline mandibulotomy has the advantage of eliminating the functional and cosmetic deficits of the lateral osteotomy or ostectomy and avoids lip paresthesia and the development of nonvital teeth secondary to injury of the inferior alveolar neurovascular bundle. A temporal approach described by Obwegeser[5] involves a well-concealed temporal incision with elevation of the facial flap in a posterior-to-anterior direction. The zygomatic arch is sectioned in two places and reflected inferiorly on a masseter muscle pedicle. The coronoid process is sectioned and reflected superiorly on a temporal muscle pedicle, providing direct access into the retromaxillary region. This approach suffers from limited anterior access. The use of the standard Weber-Fergusson approach, modified to include sectioning of the zygomatic arch and coronoid process with rotation on muscle pedicles, as described above, has also been reported by several authors.[6,7]

Neoplasms of the maxillary sinus, because of their silent nature, often present in an advanced state with extension beyond the confines of the sinus on initial presentation. High-resolution computed tomography and magnetic resonance imaging now allow accurate assessment of tumor extension, resulting in improved preoperative patient selection. Surgery in combination with radiotherapy remains the most effective treatment for these neoplasms. The morbidity of radical surgery on the maxilla has decreased significantly, allowing extensive ablative procedures to be undertaken with acceptable complication rates. Combining labiomandibulotomy with the standard anterolateral Weber-Fergusson approach provides direct access to the infratemporal and pterygopalatine fossae. This improved surgical access allows all-encompassing resections to be done in selected cases of advanced antral malignancy with posterior extension.

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The Cutaneous Scapular Free Flap in Head and Neck Reconstruction

Michael J. Sullivan, MD; William R. Carroll, MD; Shan R. Baker, MD

• Successful surgical reconstruction of complicated soft-tissue defects of the head and neck region has been greatly enhanced by free-revascularized tissue transfers. The scapular free flap has become a favored reconstructive option in our department and has been reported previously for one-stage mandibular reconstruction. This flap can also be transferred as a cutaneous free flap. We present our clinical experience with the fasciocutaneous scapular free flap and review the anatomy, surgical technique, and utility of this versatile flap.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:600-603)

Free revascularized tissue transfer has gained a solid position among the reconstructive options available to the head and neck surgeon. Restoration of form and function are often possible with single-stage microsurgical tissue transfer even in the face of a compromised recipient tissue bed. Throughout the body, there are several potential donor sites of soft tissue for head and neck reconstruction that include the radial forearm, the lateral thigh, the groin, the latissimus dorsi, the omentum, and the scapular flap. The free latissimus dorsi flap has been used in the secondary closure of orbitomaxillary defects[1] and adapted for combined palatal and midfacial reconstruction,[2] but the disadvantages of excessive bulk and donor site morbidity often limit its use to carefully selected cases.

The scapular free flap has become one of the more useful free flaps for head and neck reconstruction and currently it is our osteocutaneous flap of choice for mandibular reconstruction. The scapular flap, however, was initially described as a cutaneous free flap. The anatomy was described by Saijo,[3] and the first clinical case was reported by Dos Santos.[4] Subsequently, a number of articles have been published describing various clinical applications of the cutaneous scapular flap in extremity reconstruction.[5-7] Surprisingly little has been published on this flap in reconstruction of the head and neck region.[8] Since 1986, we have used the cutaneous scapular flap in head and neck reconstructive efforts in five patients. We outline our experience and review the anatomy, surgical technique, and use of this versatile flap.

METHODS

Anatomy

The vascular anatomy of the cutaneous scapular free flap is constant and has been well documented[3,5,6] (Fig 1). The subscapular artery arises from the third portion of the axillary artery. As the subscapular artery descends, it bifurcates to form the circumflex scapular and thoracodorsal arteries. The circumflex scapular artery courses posteriorly along the deep surface of the teres minor muscle to appear in the muscular triangle formed by the teres minor superiorly, the teres major inferiorly, and the long head of the triceps muscle laterally (the omotricipital triangle). Here, at the lateral border of the scapula, the circumflex scapular artery supplies periosteal branches to the scapula before dividing into the transverse and descending terminal cutaneous branches. As a fasciocutaneous flap, the terminal axial branches to the cutaneous scapular flap remain in the superficial layer of the dorsal thoracic fascia from which small cutaneous perforators arise to nourish the overlying skin.[9] This adds considerable versatility as we describe.

Dye injection studies in fresh cadavers have demonstrated a large cutaneous representation of the circumflex scapular artery. Generally, this region extends from the posterior axillary crease laterally to the vertebral bodies medially, and from the scapular spine superiorly to the inferior angle (tip) of the scapula inferiorly. The skin paddles can be designed to follow the transverse fasciocutaneous branches (scapular flap) or the descending fasciocutaneous branches (parascapular flap). If a large donor flap is needed, both transverse and descending systems can be preserved with the flap.

Surgical Technique

The patient is positioned in the lateral decubitus position to provide simultaneous access to the scapula and to the head and neck regions. Whenever possible, two surgical teams are employed. The arm is

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draped free into the surgical field to allow manipulation during the dissection. The lateral scapular border, the scapular spine, the inferior scapular angle, and the omotricipital triangle are located and marked on the skin. The skin paddle may be oriented transversely in the distribution of the cutaneous scapular artery or vertically in the distribution of the cutaneous parascapular artery. In most cases, the width of either flap is limited to 12 cm to allow primary closure. Limits of the scapular cutaneous flap (transverse orientation) are the scapular spine, the inferior angle of the scapular, the posterior axillary line, and the vertebral column. The parascapular cutaneous flap can be extended inferiorly. Original arterial injection studies suggest that the parascapular flap could extend 30 to 35 cm below the scapular spine. Distal to the inferior angle of the scapula, the skin becomes increasingly dependent on collateral circulation from the thoracodorsal artery.

Dissection of the scapular cutaneous flap begins medially in a plane just superficial to the deep muscular fascia of the intraspinatus muscle. The more superficial dorsal thoracic fascia must be preserved. The lateral border of the scapula is approached with caution and the dominant branches of the circumflex scapular artery are identified and preserved. Muscular and periosteal branches of the circumflex scapular artery are ligated as the pedicle is followed over the lateral border of the scapula. The vascular pedicle is followed into the axilla and the muscles of the omotricipital triangle are retracted. Occasionally the blood supply to the latissimus dorsi muscle is intentionally preserved and the circumflex scapular vessels are divided distal to the origin of the thoracodorsal vessels, recognizing that this limits the length of the vascular pedicle from 6 to 7 cm. More often, however, the thoracodorsal vessels are sacrificed and the vascular pedicle to the flap is divided proximally at the origin of the subscapular trunk from the axillary vessels.

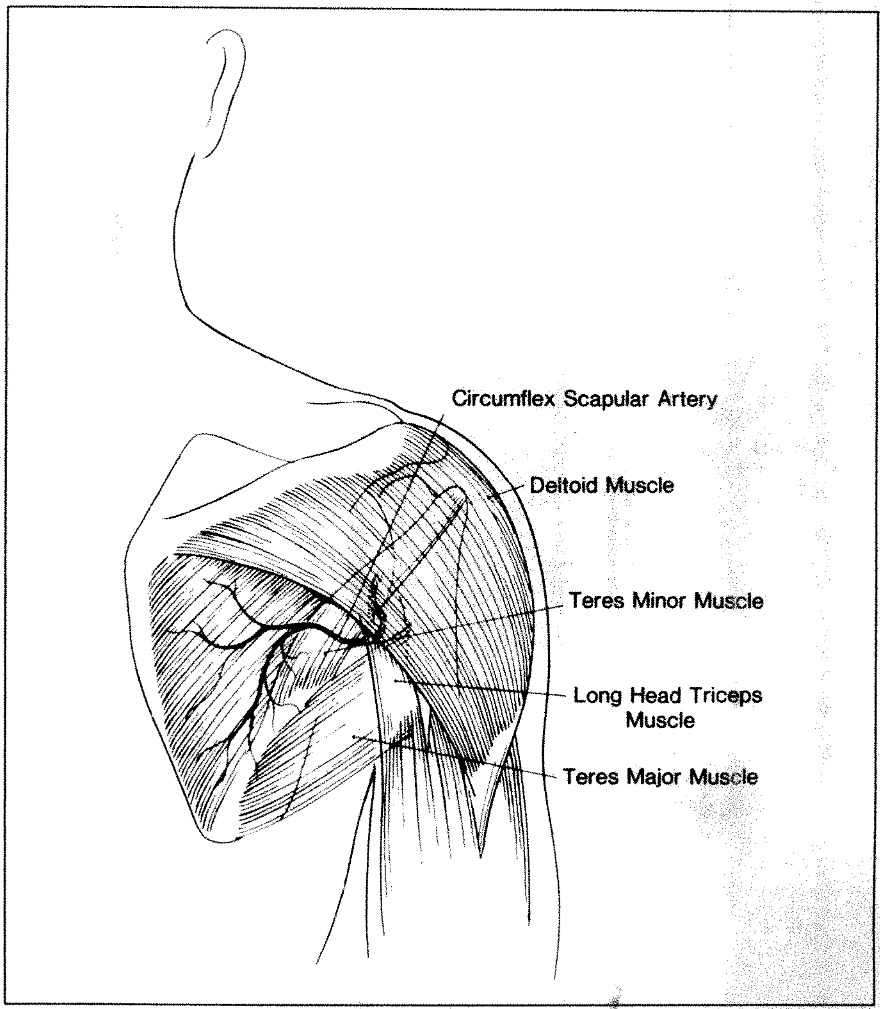

Fig 1.—Vascular anatomy of the scapular region.

Clinical Application

Since 1986, we have successfully used the cutaneous scapular free flap in the reconstruction of five patients. Each of the five cases is presented briefly. The donor sites were closed primarily in each of these cases and none of the patients experienced donor site morbidity as a result of the tissue transfer.

REPORT OF CASES

CASE 1.—A 61-year-old man developed a basal cell carcinoma of the right side of the face in the late 1950s, which was treated with surgical excision followed by radiation therapy. The lesion recurred in 1970, but the patient sought no further care until 1986. On presentation, there was a 12 × 12-cm lesion of the right frontal scalp and orbit, requiring wide excision and orbital exenteration. A 10 × 15-cm right scapular cutaneous flap was harvested to cover the facial and scalp defect and a split-thickness skin graft was applied to the remaining orbital bone (Fig 2). The patient has been free of recurrence for 2 years.

CASE 2.—A 59-year-old woman had a carcinoma of the left mandibular alveolus resected in 1983 followed by a recurrence treated with radiation in 1984. She presented with a presumed second primary of the left buccal mucosa in 1987, requiring full-thickness excision, including cheek skin. A 6 × 8-cm scapular cutaneous flap was harvested to close the cheek and buccal defects.

CASE 3.—A 69-year-old woman had a basal cell carcinoma removed from the left forehead in 1986. The lesion recurred aggressively and excision required removal of both tables of the left frontal sinus and an orbital exenteration. An 8 × 15-cm left scapular cutaneous flap was used to fill the entire defect (Fig 3).

CASE 4.—A 63-year-old man developed an extensive basal cell carcinoma of the left temporal region. In 1983, a resection was performed, including a total parotidectomy, partial mandibulectomy, and a lateral temporal bone resection. The lesion was initially covered with a split-thickness skin graft. Two years later, a scapular cutaneous flap was employed to cover the entire defect. He remains free of recurrence.

CASE 5.—A 35-year-old woman had Wegener's granulomatosis with extensive involvement of the right maxillary sinus, the pterygomaxillary space, and the floor of the orbit. Her disease was refractory to aggressive medical therapy, and, in 1986, she required a right-sided maxillectomy and orbital exenteration. Following healing of the cavity and with the Wegener's granulomatosis in remission, a 6 × 6-cm right scapular cutaneous flap was used to fill her orbitomaxillary defect (Fig 4). Ablation of the large cavity has allowed improved speech and deglutition and support for an orbital prosthesis.

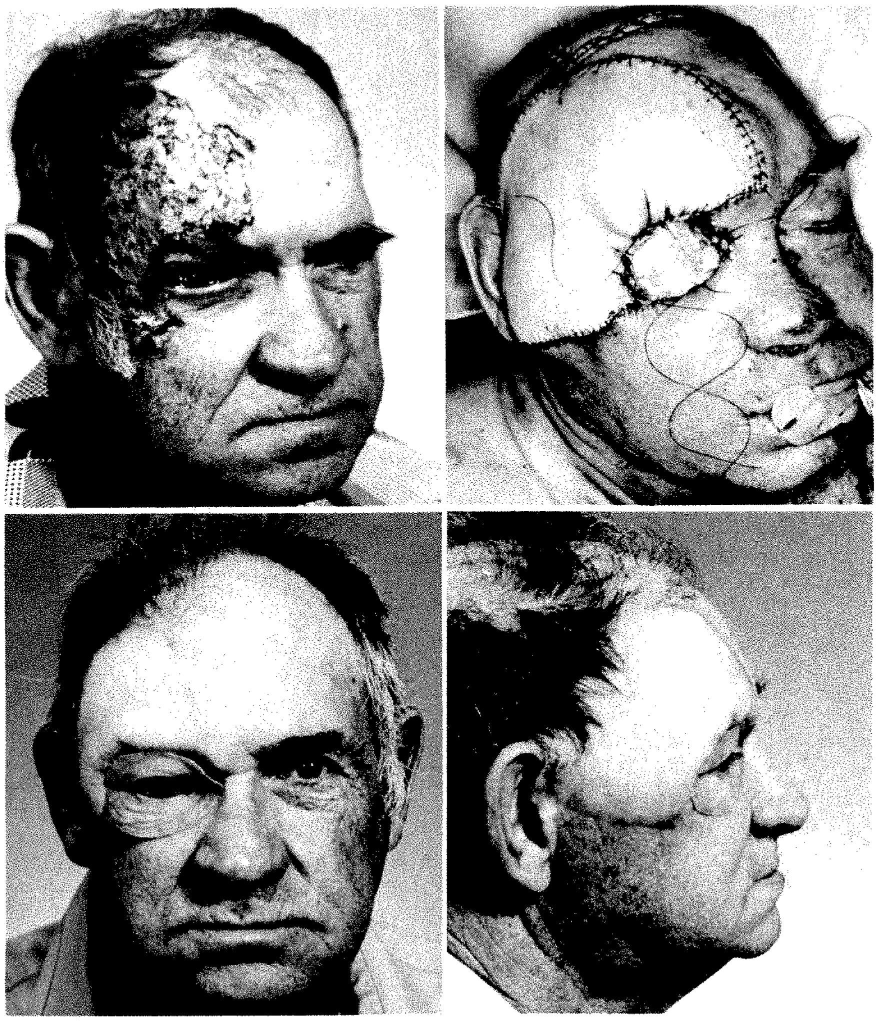

Fig 2.—Top left, Preoperative photograph of patient with extensive basal cell carcinoma of the scalp and orbit. Top right, Primary reconstruction with a 10 × 15-cm scapular cutaneous flap. Bottom left, Anterior view after flap debulking and orbital prosthesis. Bottom right, Lateral view.

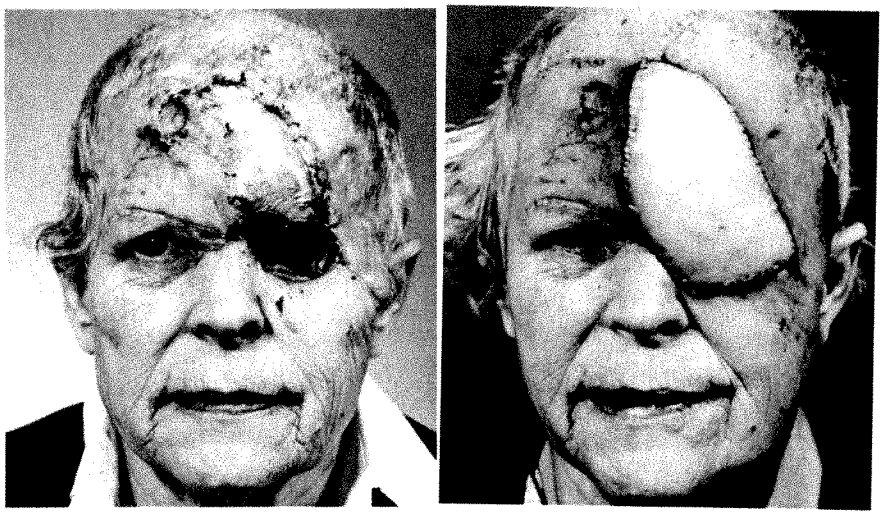

Fig 3.—Left, Postoperative photograph of patient after resection of scalp and orbital basal cell carcinoma and split-thickness skin graft coverage. Right, Following coverage with 8 × 15-cm scapular cutaneous flap. Patient will require second-stage debulking procedure.

COMMENT

The widespread clinical application of microvascular techniques and free tissue transfer have greatly expanded our armamentarium for reconstruction of head and neck soft-tissue defects. The plethora of potential donor sites and the continuing definition of new vascular territories, however, can make flap selection confusing. The microsurgeon should become familiar with the different flaps, but expertise with two or three flaps will ordinarily suffice for most circumstances. We have found the scapular cutaneous free flap to be an especially versatile soft-tissue flap that we were able to adapt for the reconstruction of a variety of head and neck defects.

The scapular cutaneous free flap has a predictable vascular anatomy that facilitates its dissection. Harvesting the flap is relatively easy and can often be completed in approximately 1 hour. With the patient in the lateral decubitus position, the scapular flap can be harvested as a separate team works in the head and neck region. The dissection, however, may be tedious in overweight patients who have a generous amount of subcutaneous tissue. This situation may prevent simultaneous flap harvesting and recipient site preparation.

The subscapular vessels are "macrovascular" in size with an average diameter of 2.5 to 4.0 mm and are an excellent match for most recipient vessels in the neck. A generous pedicle length of 7 to 10 cm facilitates reconstruction of scalp and facial soft-tissue defects, with the vessel anastomosis in the neck (Fig 5). The flap does not have an accompanying sensory nerve, which may be a disadvantage if sensate skin is desired.

A generous donor area is available with the potential for an enormous amount of tissue for transfer, particularly when the scapular and parascapular cutaneous paddles are harvested simultaneously. The skin of the upper back is often lax and pliable and the donor site would be expected to be

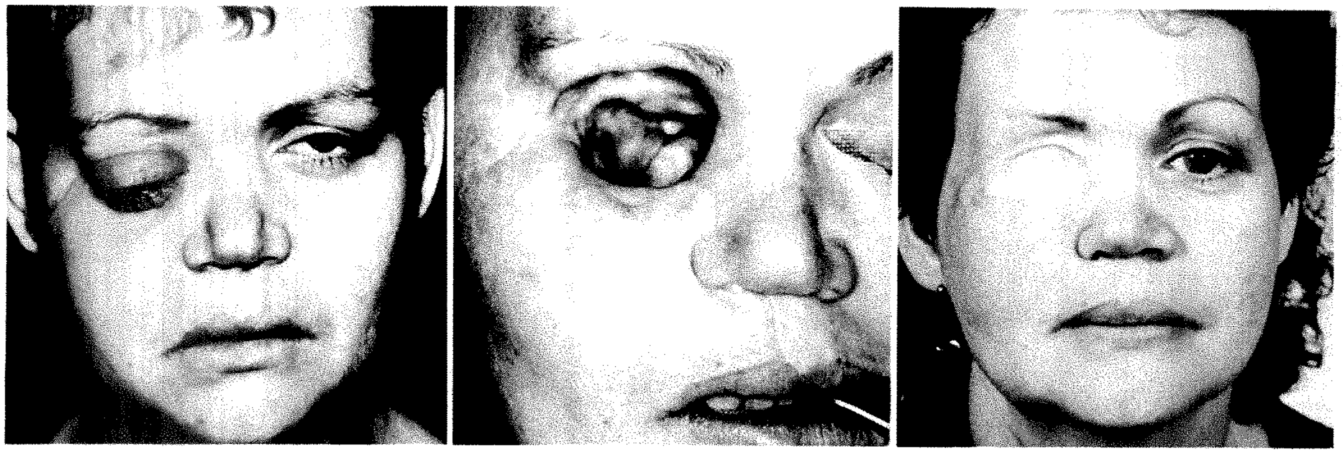

Fig 4.—Left, Patient with Wegener's granulomatosis involving the orbit and maxillary sinus. Center, Orbital exenteration cavity. Right, Scapular cutaneous flap reconstruction result after debulking.

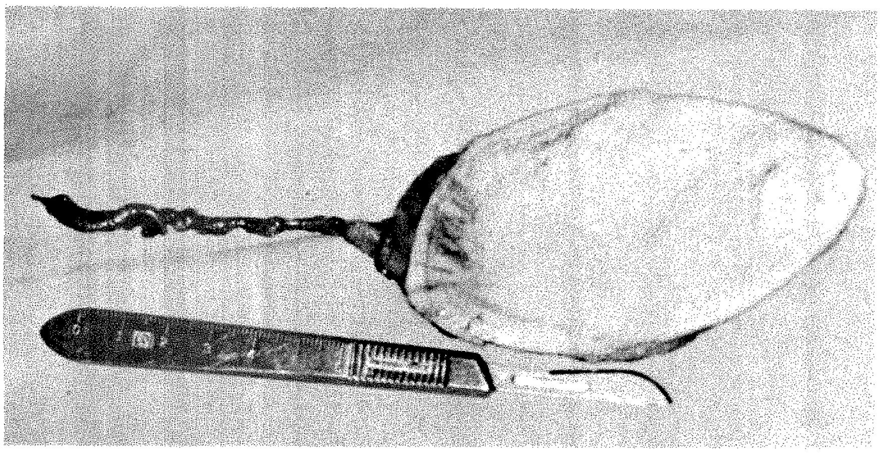

Fig 5.—Scapular cutaneous flap with generous pedicle length.

closed primarily in most circumstances. The closure, however, may be under tension after harvesting a large flap and result in a wide and unsightly scar. The scapular cutaneous free flap also has the advantage of being harvested with the latissimus dorsi muscle based on the thoracodorsal branch of the subscapular vessels for extremely large defects.

Shoulder morbidity does not occur when the scapular cutaneous free flap is harvested as long as the three nerves that are commonly encountered in the dissection, the nerve to the teres major, the thoracodorsal nerve, and the long thoracic nerve are not disrupted. All of our patients are seen preoperatively by the physical therapist and followed up postoperatively to ensure full shoulder rehabilitation.

The bulkiness of the scapular cutaneous free flap is dependent on the thickness of the back skin and subcutaneous tissue. It can be rather bulky in some individuals. The flap is intermediate in thickness between the thin radial forearm flap and the bulky latissimus dorsi myocutaneous flap. The subcutaneous fat of the scapular cutaneous free flap can be advantageous in situations requiring more soft-tissue augmentation. For head and neck defects requiring smaller amounts of thin tissue, like the face, the cutaneous scapular flap may require secondary debulking or liposuction. The radial forearm flap may actually be preferable in this situation.

As a fasciocutaneous flap, the skin of the scapular cutaneous flap can be incised and the flap folded on itself for combined external and internal oral defects. All, or a portion of, the skin can be deepithelialized for deep-tissue augmentation. Typically, a small strip of skin is retained with the flap as an indicator of viability.

The cutaneous scapular free flap has many desirable features for reconstruction of large soft-tissue defects of the head and neck. A large volume of tissue can be harvested quickly with minimal donor site morbidity. The flap is intermediate in thickness, which may be of advantage for augmentation purposes, but may require secondary debulking or liposuction when used on the face. As a fasciocutaneous flap, the skin of the scapular cutaneous flap can be incised or deepithelialized to fit most defects.

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Is Papillomavirus Detectable in the Plume of Laser-Treated Laryngeal Papilloma?

Allan L. Abramson, MD; Teresa P. DiLorenzo, MA; Bettie M. Steinberg, PhD

• The carbon dioxide laser is widely used for the vaporization of lesions in patients with laryngeal papillomatosis. In this study, the smoke plume resulting from the laser treatment of laryngeal papillomas was analyzed for the presence of human papillomavirus DNA. Plumes were collected with a suction tip and trapped in phosphate-buffered saline. The aspirates were then analyzed for the presence of human papillomavirus DNA by Southern blot hybridization. Human papillomavirus DNA cannot be detected in the smoke plume from vaporization of laryngeal papillomas unless direct suction contact is made with the papilloma tissue during surgery. The implications of these findings are discussed.

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Papillomas are the most common benign neoplasms of the larynx in children, but they have an equal propensity to occur in adults. They characteristically present as single or multiple exophytic masses most commonly located on the true vocal cords, but may also involve the supraglottic and subglottic regions. Clinically, the initial symptoms are hoarseness or an abnormal cry, and subsequently respiratory distress and stridor. Repeated endoscopic surgery is frequently needed to remove the papillomas and may result in scarring of the larynx and a loss of normal vocal function.

Laryngeal papillomas are caused by one or more of the human papillomaviruses (HPVs). This group of related epitheliotropic DNA viruses also causes cutaneous warts and genital condylomata. There are currently more than 50 known HPVs that show a predilection for involvement of specific tissue sites.[1] The HPVs found in the larynx are type 11 and, to a lesser degree, the closely related type 6. Common skin warts usually contain HPV 2, while palmar and plantar warts contain HPVs 1 and 4. It is important to note that HPV types 6 and 11 do not cause cutaneous warts, nor do HPVs 1, 2, or 4 cause laryngeal papilloma.

Currently, the carbon dioxide laser is widely used to remove the lesions of patients with laryngeal papillomatosis.[2] The emission wavelength of 10 600 nm permits conversion of the light energy to thermal energy when absorbed by water in the tissues. The result is a controlled destruction of the tissue, with vaporization of the water, effective cautery of the tissue surface, and generation of a smoke plume that contains the water vapor and destroyed tissue material. The use of this procedure has facilitated the management of laryngeal papillomatosis.

A recent report described the detection of papillomavirus DNA in the smoke plume resulting from carbon dioxide laser use.[3] Two types of lesions were studied. An in vitro study was performed on cutaneous bovine warts (caused by a bovine papillomavirus) that had been surgically removed from cattle and brought to the laboratory. Also, an in vivo study was carried out on seven patients with plantar or mosaic warts that had been recalcitrant to other therapies or were extensive in size.

Both cutaneous bovine warts and human plantar warts are characterized by extremely high numbers of copies of papillomavirus DNA in the lesions, averaging several hundred per cell. In contrast, laryngeal papillomas usually have an average of only 1 to 50 copies per cell, with most lesions containing fewer than 10 copies per cell.

The goal of this study was to investigate whether HPV DNA can be detected in the smoke plume that results from the carbon dioxide laser therapy of laryngeal papilloma.

MATERIALS AND METHODS

Clinical Techniques

Anesthesia was maintained using intermittent intravenous agents. A continuous

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succinylcholine infusion was used to provide muscle relaxation. After this was achieved, an Abramson-Dedo laryngoscope was introduced and placed just proximal to the area of involvement with laryngeal papilloma. A 14-gauge blunt metal ventilating needle was then introduced into one of the four available laryngoscope channels and placed below the vocal cords. The Sanders injector was attached to the ventilating needle and inflation of the lungs performed. The driving pressure varied between 15 and 40 psi.

The operating microscope with the carbon dioxide laser was brought into position and focused to allow a magnified view of the larynx.

Clinical Protocol

Seven patients (five children and two adults) with multiple recurrent laryngeal papillomas entered this study. During the experiment, a 3-mm open-tipped, 24-cm (in length) laryngeal suction tube was directly attached to a sterile collecting trap into which phosphate-buffered saline (PBS) was placed and connected to the operating room vacuum system (375 mm Hg). The entire suction apparatus was subsequently changed to a completely sterile setup for each phase of the investigation.

In one patient, the suction tip was placed on the papilloma and gently moved over the surface for 10- and 30-second intervals. The contents were collected into a PBS trap. The laser was not in use while this specimen was collected.

In six patients, the suction tip was carefully placed 5 to 10 mm above the papilloma and the laser smoke plume collected into PBS. During this phase the laser was set at 9 W in a continuous mode for 30 seconds.

During the last investigation in five of the six patients, the suction tip was then deliberately and intermittently touched to the surface of exophytic laryngeal papillomas and the plume collected. The laser was set at 9 W in a continuous mode for 60 seconds.

Other Methods

To document the presence or absence of intact epithelial cells, a slide was prepared from one tenth of the volume of most PBS specimens using a centrifuge (Cytospin 2, Shandon Southern Instruments, Sewickley, Pa). The particulate matter was spun down onto a slide at 400 rpm for 10 minutes, fixed with phosphate-buffered 4% formaldehyde solution, and stained with hematoxylin-eosin.

The remainder of each specimen was adjusted to a final concentration of 0.6% sodium dodecyl sulfate, 10-mmol/L ethylenediaminetetraacetate, and 50-μg/mL proteinase K. Samples were incubated at 55°C for 1 hour. The samples were extracted once with an equal volume of phenol (equilibrated with 0.3-mol/L sodium acetate), once with a mixture of phenol/chloroform/isoamyl alcohol (25:24:1), and once with chloroform/isoamyl alcohol. Two volumes of ethanol and 3 μg of sheared salmon testes carrier DNA were added to each sample, and DNA was precipitated at −20°C overnight. The DNA was pelleted by centrifugation, washed with 70% ethanol, dried, and resuspended in 10-mmol/L TRIS hydrochloride (pH 8)/5-mmol/L magnesium chloride/100-mmol/L sodium chloride/1-mmol/L β-mercaptoethanol. Samples were then digested with *Bam*HI at 37°C for 2 hours.

The DNA was electrophoresed through 0.9% agarose gels and blotted onto nylon membranes (Gene Screen Plus, New England Nuclear Research Products, Boston, Mass) according to the method of Southern.[4] The blots were hybridized at 42°C overnight in 50% formamide/0.75-mol/L sodium chloride/0.075-mol/L sodium citrate/5× Denhardt's solution/50-mmol/L sodium phosphate (pH 6.8)/1.5% sodium dodecyl sulfate/250-μg/mL sheared salmon testes DNA/1×10^6-cpm/mL DNA probe. The probes used were cloned HPV-11 DNA labeled by random priming[5,6] or cloned HPV-6 DNA labeled by nick translation[7] to a specific activity of greater than 1×10^8 cpm/μg with [α-^{32}P]deoxycytidine-5′-triphosphate. The blots were first washed in 2× SSC (1× SSC is 0.15-mol/L sodium chloride/0.015-mol/L sodium citrate) at room temperature, then in 2× SSC/1% sodium dodecyl sulfate at 68°C, and finally in 0.1× SSC at room temperature. (These hybridization and wash conditions allow HPV 11 and HPV 6 to cross-hybridize.) The filters were wrapped in plastic wrap and exposed to film (Kodak XAR5, Eastman Kodak, Rochester, NY) at −70°C using intensifying screens.

RESULTS

Specimens were processed from the laser surgeries of seven patients with laryngeal papillomas. They consisted of aspirates collected when the suction tip was carefully placed to remove the smoke plume without contact with the tissue. This was followed by a specimen collected when the tip was deliberately touched to the papilloma during the laser procedure, an event that occurs routinely. In most cases, both specimens were available from the same patient. The results are shown in Fig 1.

Lanes 1 and 2 in Fig 1 contain 50 and 5 pg of cloned HPV DNA, respectively. These lanes provide molecular markers and means for estimating the sensitivity of the hybridization. Lanes 4, 7, 9, 12, and 13 contain extracts of the smoke plumes when no contact with the tissue was permitted. In no case was HPV DNA detected, even on very long exposure. Lanes 8, 10, 11, and 14 are "touch specimens" corresponding to the patients in lanes 7, 9, 12, and 13, respectively. Clearly, if the probe touched the tissue, DNA could be detected in the material aspirated by the suction device. Lanes 5 and 6 were extracts of a light and heavy touch of the same patient seen in lane 4. Lane 6 was positive on a much longer exposure, but lane 5 remained negative. We conclude that not all probes that touch the lesion during the laser surgery become contaminated with the HPV. Lane 3 contains material from the suction device when the probe was touched to the papilloma but the laser was not active. This material also contained HPV DNA. It appears that the determining factor is contact with the tissue itself, and that contamination of the aspirate is unrelated to laser use.

To determine whether the aspirates collected when tissue was touched contained cellular debris, a portion was analyzed microscopically. The aspirates from the smoke plumes contained no identifiable cellular materials. In contrast, the aspirates from when the suction tip made contact with the tissue contained red blood cells, lymphocytes, and most important, superficial cells from the papilloma (Fig 2). (The specimen shown in Fig 2 is the same specimen shown in Fig 1, lane 10.)

COMMENT

We have demonstrated that HPV DNA cannot be detected in the smoke plume from vaporization of laryngeal papillomas unless direct suction contact is made with the tissue during surgery. These results differ from those recently reported by Garden et al,[3] in which they describe the detection of papillomavirus DNA in the smoke plume resulting from the vaporization of cutaneous bovine fibropapillomas and human plantar and mosaic warts. These lesions are char-

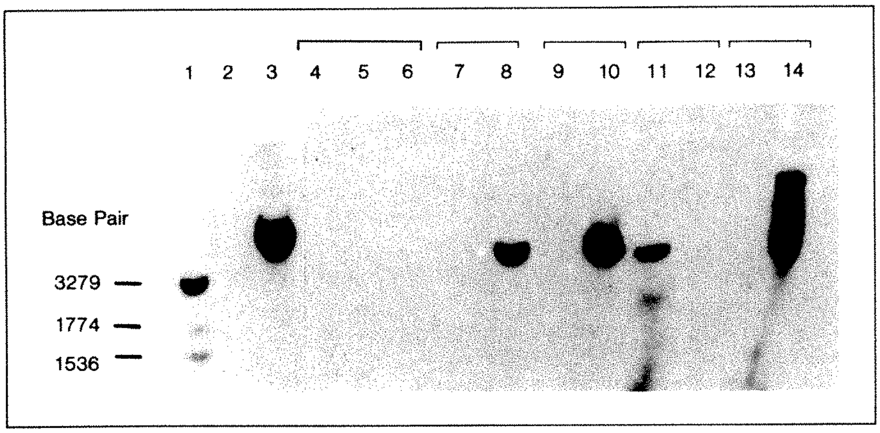

Fig 1.—Southern blot of laryngeal phosphate-buffered saline aspirates. Lanes 4, 7, 9, 12, and 13 represent plumes with no suction contact; lanes 3, 5, 6, 8, 10, 11, and 14, deliberate suction contact with papilloma; lane 3, laser not used; and lanes 1 and 2, human papillomavirus standards with 50 and 5 pg of DNA, respectively. Bracketed lanes represent the same patient.

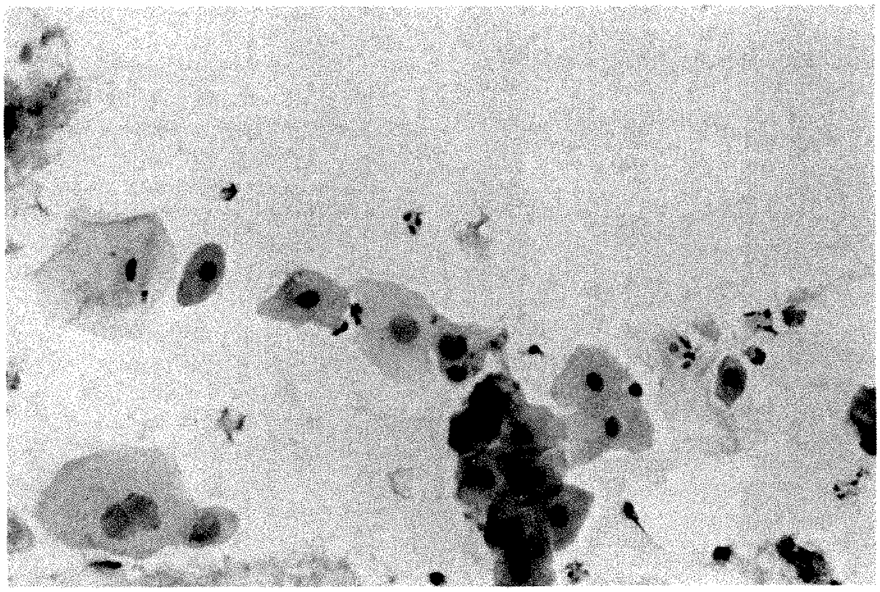

Fig 2.—Microscopic appearance of a plume collected when the suction tip was touched to the laryngeal papilloma (hematoxylin-eosin, ×90).

acterized by high numbers of papillomavirus particles, averaging several hundred to several thousand per cell. This is in contrast to laryngeal papillomas, of which many specimens contain low numbers of copies of viral DNA but no virus particles. Since the superficial cells of bovine and human cutaneous warts contain high numbers of viral particles, it is important to know if the suction tip was permitted to touch the surface of the papilloma during collection of the laser plume. This information was not stated. If any of the squames from the lesion were directly aspirated, they would serve as the source of papillomavirus DNA.

The papillomaviruses only replicate to produce new viral particles in the well-differentiated cells near the surface of stratified squamous epithelium. It would therefore be expected that the superficial cells from these lesions would contain more virus per cell than the average for the papilloma, and that a relatively small amount of superficial tissue would have detectable levels of HPV DNA.

In our study using Southern blot analysis, it was not possible to determine whether the material aspirated when the tip made contact with the tissue existed as viral particles or as free DNA. However, it is likely that most of it did not exist as the former. When HPV infects the larynx, one of two things can occur. The infected cells are latent and show no change,[8] or the viral DNA causes the transformation of the epithelial cells to form a papilloma. It is rare for any of the cells in the papilloma to produce infectious virus. Latent infections never do. Immunohistochemical stains of laryngeal papillomas for viral proteins are frequently negative.[9] Therefore, surgical manipulations or other procedures probably do not "seed" virus. The carbon dioxide laser was used between 1978 and 1986 in conjunction with jet ventilation in 393 procedures in juvenile-onset and 146 procedures in adult-onset laryngeal papillomatosis with no subsequent seeding of the trachea or lung parenchyma.[2]

An intact papillomavirus particle contains DNA that is tightly packaged within a protein coat. It is the interaction of this protein coat with receptors on the surface of the epithelial cell that permits the entry of the virus into the cell. Naked DNA released from the virus, or DNA from within a cell that was not packaged within a viral particle, lacks the protein required for attachment to the cell. Moreover, the large tangled mass of DNA is easily fragmented and is normally not infectious.

Even in the laboratory, it is difficult to infect cultured cells with naked viral DNA. To do so, it is necessary to treat the DNA with calcium phosphate. Under these conditions the DNA precipitates onto the cells and sticks to the cell membrane. It can then be taken up by the cell. This process is very inefficient compared with a normal virus infection. With SV40, a DNA virus in the same family as the papillomaviruses, comparisons of efficiency between the two types of infections have been done. When cells are infected with viral particles, an average of one particle per cell is necessary to detect the infection. In contrast, under optimal conditions in which a special type of cell is used that nonspecifically takes up DNA better than most cells, more than 10 million molecules per cell are required for 40% of the cells to be positive.[10] Clearly, DNA is not normally infectious, while viral particles are.

In our study, since contact of the suction tip with the papilloma tissue resulted in epithelial cells in the aspirate, we must assume that at least some of the aspirates contained intact viruses. These would be infectious. HPVs 6 and 11, which cause laryngeal papillomas, only infect mucous membranes and genital tissues. Therefore, developing a cutaneous wart on the hand or face from contact with this material is virtually impossible. Warts in these areas normally contain HPVs 1, 2, and 4, and HPVs 6 and 11 have never been described as the cause of cutaneous warts. Infection with HPV 6 or the closely related HPV 11 does appear to be responsible for most of the ocular conjunctival papillomas of children and young adults.[11]

During endolaryngeal surgery for laryngeal papillomas, appropriate eye protection, masks, and gloves must be worn throughout the procedure. Since the aspirate should be treated as potentially infectious material, suction canisters and connecting tubing must be disposable and changed for each case.

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IN OTHER AMA JOURNALS

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Recurrent Meningitis and Mondini Dysplasia

Laurie A. Ohlms, MD; Morven S. Edwards, MD; Edward O. Mason, MD;
Makoto Igarashi, MD; Bobby R. Alford, MD; Richard J. H. Smith, MD

• Three infants with cerebrospinal fluid otorrhea and recurrent meningitis due to Mondini dysplasia have been treated at Baylor College of Medicine, Houston, Tex; 39 other patients with this association have been described. This review highlights the characteristics and embryologic basis of the malformation. The clinical evaluation of an infant with recurrent meningitis is outlined, and the importance of brain-stem response audiometry and thin-cut computed tomography of the temporal bones is discussed. Surgical management depends on the functional status of the dysplastic ear; usually, a stapedectomy is performed and the vestibule is obliterated. Although the surgical failure rate is 30% after one procedure, early identification of the dysplasia and prompt surgical management diminish morbidity and mortality and permit early habilitation of the child with congenital hearing impairment.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:608-612)

Four major patterns of congenital inner ear malformation are commonly recognized. These patterns represent points along a continuum, making specific "classification" of a given anomaly often difficult. The most severe aplasia, the Michel, is characterized by complete failure of inner ear development. Incomplete formation of the bony and membranous labyrinths is known as Mondini dysplasia. Scheibe dysplasia, the most commonly encountered, is characterized by abnormal development of only the membranous pars inferior. Alexander dysplasia is the least severe type of malformation and consists of aplasia of the cochlear duct; usually only the basal turn is affected.

Typically, these malformations are associated with some degree of hearing impairment. In addition, the Mondini malformation can be associated with cerebrospinal fluid (CSF) otorrhea and recurrent meningitis. Three patients with this defect have been seen at Baylor College of Medicine, Houston, Tex. Two have been previously described and are briefly discussed here; the third is described in detail.[1, 2] The morphological features, clinical presentation, and treatment options are described.

REPORT OF CASES

CASE 1.—An 18-month-old boy was seen after his second episode of pneumococcal meningitis. Hearing was absent in the right ear with only minimal low-frequency responses present in the left. Physical examination revealed a pale, bulging right tympanic membrane; following a right myringotomy, a profuse flow of clear fluid was noted. Middle ear exploration confirmed CSF leaking from the oval window. The incus and stapes were removed, and the enlarged vestibule was packed with temporalis fascia. A small piece of cortical bone was used to "cork" the oval window, and the middle ear was packed with Surgicel. Recovery was uneventful. At the age of 9 years, the patient suffered a third attack of meningitis; evaluation at that time failed to reveal a CSF leak.

CASE 2.—A 1-year-old boy presented with pneumococcal meningitis and bilateral acute suppurative otitis media. After bilateral myringotomies, pus, followed by a copious flow of CSF, was noted in the right ear. Auditory testing showed no response in that ear, although in the left a response was obtained at 60-dB hearing loss. Computed tomography confirmed bilateral Mondini malformations. At surgery, CSF was leaking from a perforation in the anterior stapes footplate and round-window membrane. The incus and stapes were removed, and the large dilated vestibule was packed with temporalis fascia; the oval and round windows were blocked with conchal cartilage. Recovery was uneventful.

CASE 3.—A 15-month-old boy was seen at Texas Children's Hospital, Houston, after his second episode of meningitis. By history, he was a term infant who weighed 3.4 kg and was delivered by cesarean section. Meconium staining and aspiration occurred at birth, and he was placed on a ventilator for the first 2 days of life. By day 4, he was discharged from the hospital. He did well until 1 year of age, when he developed pneumococcal meningitis after an episode

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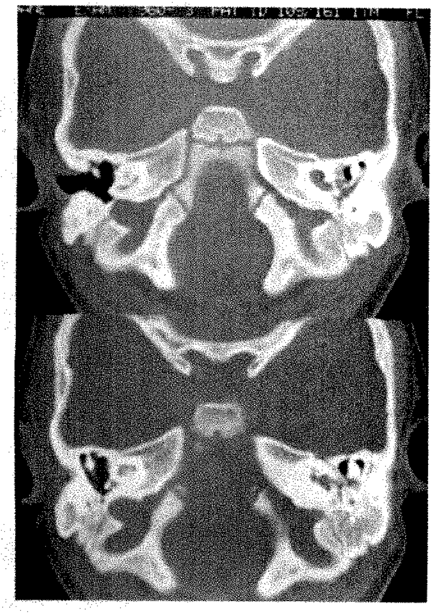

Fig 1.—Thin-cut computed tomographic scan showing characteristic appearance on Mondini malformation (left).

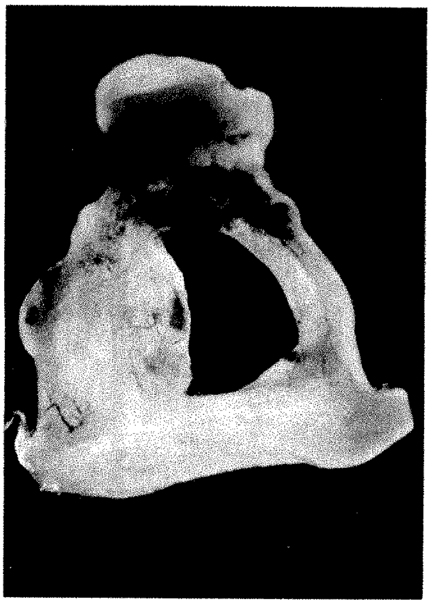

Fig 2.—High-power view of the stapes showing mucosal sac arising from footplate (case 3).

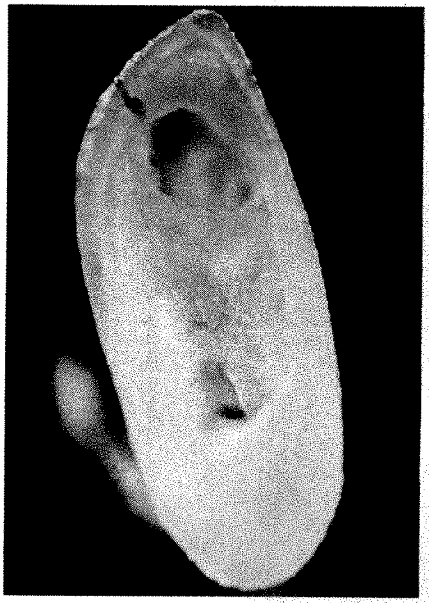

Fig 3.—Defects in stapes footplate (case 3).

of otitis media. This episode resolved with ampicillin sodium therapy. Over the next 2 months, a continuous regimen of oral antibiotics was used to treat persistent otitis media with effusion. In late January 1988, the patient developed another episode of acute otitis media, again followed by pneumococcal meningitis. He was transferred to Texas Children's Hospital for further evaluation.

Physical examination confirmed the presence of a left serous otitis. The white blood cell count was elevated to 19 × 10⁹/L, and cultures of blood and CSF yielded *Streptococcus pneumoniae*. Thin-cut computed tomographic scanning revealed a Mondini malformation of the left ear, and auditory testing showed no response to air or bone conduction on that side (Fig 1).

Exploration of the left middle ear revealed a fluid-filled mucosal sac obscuring the stapedial footplate; clear fluid was leaking from the sac. Following stapedectomy, the enlarged vestibule was obliterated with temporalis muscle and fascia; the incus, used to cork the oval window, was anchored in position by the malleus. Inspection of the stapes showed an oval-shaped bony defect in the footplate (Figs 2 and 3). Postoperatively, the patient did well and has had no further episodes of meningitis.

COMMENT

In 1791, Carlo Mondini[3] presented a paper before the Academy of Sciences of the University of Bologna (Italy) entitled, "An Anatomical Dissection of a Boy Born Deaf." He described an 8-year-old boy, born deaf, who developed gangrene after he was struck on the foot by a wagon; in a few days, he died. Mondini immediately applied himself "to the examination of the organs of hearing, and . . . was careful to the utmost of [his] ability that not even the smallest part should escape [his] diligent scrutiny." He noted that the external and middle ears appeared normal but, "As regards to the vestibule, there was nothing in its shape which indicated any defect, except that it had acquired a greater than normal size." The cochlea "was exceedingly flawed. According to its nature it makes in its ascent two and one-half spirals, and in our boy who was born deaf it completed only one and one-half with the final spiral at the apex missing, and it ended in a large hollow corresponding to the cavity of the final spiral." This is the first description of combined membranous and bony dysplasia based on an anatomical dissection of the inner ear.

In 1904, Alexander[4] described the histologic features found with this type of malformation, and Siebenmann[5] reported another case of incomplete cochlear development associated with congenital deafness. He named the defect after Mondini. Twenty-three years later, Fraser[6] presented a report of a child with bilateral Mondini malformation to the Royal Society of Medicine. His clinical description suggests that the child had the Wildervanck form of the Klippel-Feil syndrome. These temporal bone sections now reside in the collection at the University of Zurich (Switzerland).

Several temporal bone studies have confirmed the pathologic changes described by Mondini.[7-9] Characteristically, the cochlea is flattened and shortened, with 1 to 1½ turns instead of the normal 2½ to 2¾ turns. Only the basal turn of the cochlea is fully developed; the upper turns form a common cavity known as the scala communis, or the cloaca. The modiolus and osseous spiral lamina are hypoplastic, and the cochlear duct is at times dilated and shortened. The stria vascularis may be atrophied. The organ of Corti is often absent, especially in the upper parts of the cochlea, and the number of spiral ganglion cells are decreased. The endolymphatic duct, vestibule, and semicircular canals can be enlarged; in extreme cases, the vestibule has a cystlike appearance (Fig 4). Many patients also have an abnormal stapes. As in cases 2 and 3, there may be an anatomical defect in the footplate; occasionally, the stapes is totally absent.

Patients with Mondini dysplasia are predisposed to developing a CSF leak.

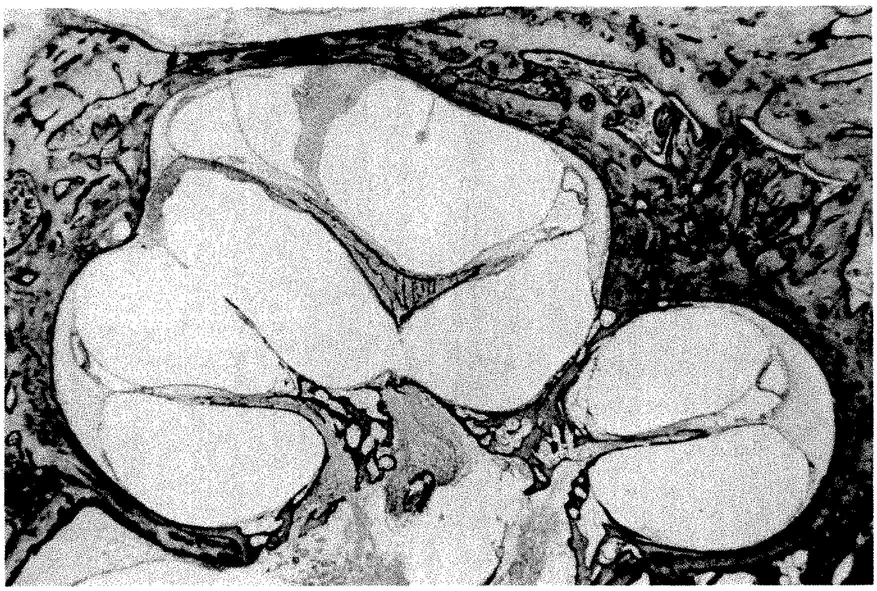

Fig 4.—Temporal bone section demonstrating typical findings of Mondini malformation.

For this to occur, two abnormalities must exist. On the medial aspect of the labyrinth, CSF must flow quickly from the subarachnoid space into the perilymphatic space. On the lateral aspect of the labyrinth, it must then escape into the middle ear through a defect in the otic capsule. The cochlear aqueduct and the internal auditory canal are two commonly acknowledged routes from the subarachnoid space to the labyrinth. Abnormalities of either can increase CSF flow into the labyrinth. A wide, patent cochlear aqueduct allows CSF to pass directly to the scala tympani, malformed cochlea, and cystlike vestibule. Flow through the internal auditory canal is possible if the lamina cribosa is thin and fragile, as noted in some cases of Mondini dysplasia.[9]

From the inner ear, CSF can leak through a defect in the otic capsule into the middle ear. The most common site of leakage is the oval window or stapes footplate, although defects have been reported in the round window, eustachian tube, promontory, fallopian canal, and hypotympanum.

Embryologically, Mondini dysplasia results from arrested development during the seventh week of fetal life. Early in the fourth week, the otic placodes, thickened plates of surface ectoderm, appear on either side of the developing hindbrain. As each placode sinks into the underlying mesenchyme, an otic pit forms. The edges of each pit fuse to create the otocyst, the precursor of the membranous labyrinth. A hollow diverticulum grows out from this structure and elongates to form the endolymphatic duct and sac.

The otocyst then differentiates into a dorsal, or utricular, portion and a ventral, or saccular, portion. Three flat diverticula grow from the utricular portion; their central parts fuse and disappear while the peripheral portions become the semicircular ducts. This process is complete by the seventh week of gestation. Concomitantly, an outgrowth appears from the ventral saccular portion of the otocyst. It develops by spiral growth to become the cochlear duct. The duct reaches its full length, 2½ to 2¾ turns, by the 10th week.

The mesenchyme around the otocyst condenses and differentiates into the cartilaginous otic capsule. As the membranous labyrinth enlarges, vacuoles appear in the otic capsule and coalesce to form the perilymphatic space. The cartilaginous otic capsule then ossifies to form the bony labyrinth of the inner ear.

Interruption in this orderly progression results in a continuum of inner ear malformations. An insult in a 4 week embryo leads to the Michel defect. An arrest at the end of the seventh week leads to a classic Mondini defect, with the cochlea represented by a short curved tube. The Scheibe and Alexander defects are the result of developmental arrests at later times.

The stapedial footplate defect also has a developmental origin. The footplate consists of two layers: an outer lamina derived from Reichert's cartilage; and an inner lamina, the vestibular layer, or lamina stapedius, formed from the otic capsule. The initial cartilaginous form of the stapes is replaced by three layers of bone: outer and inner periosteal layers, with an endochondral layer in between. The bone is then remodeled in a resorptive fashion (23 to 26 weeks) to thin the crura and to enlarge the obturator foramen.

The vestibular layer of footplate cartilage does not undergo bony replacement, but is preserved as a base on which the outer bony layer of the footplate is deposited. If the vestibular layer of cartilage does resorb, a defect results. The outer layer of bone lacks a cartilaginous base and develops as only a monomeric membrane spanning the breadth of the footplate. A fistula from the vestibule to the middle ear space then results.

The child with Mondini malformation may present to the otolaryngologist in several ways. If the malformation is bilateral, profound sensorineural hearing loss may be the initial sign of a congenital defect. If the malformation is unilateral, the dysplasia may go undiagnosed for years. Occasionally, patients with normal hearing have been reported, but more frequently, the Mondini ear is clinically unreactive, having neither cochlear nor vestibular function.

When a CSF leak develops, findings depend on the functional status of the involved ear. If there is residual auditory function, a sudden or fluctuating sensorineural hearing loss may occur. With residual vestibular function, the patient may experience vertigo and have a positive fistula test. A CSF effusion in the middle ear may cause rhinorrhea or otorrhea. More commonly, however, the effusion is asymptomatic and does not cause a perceptible conductive hearing loss, because the ear is nonfunctional. The gravity of the problem than may remain undetected until a myringotomy is performed, releasing a profuse flow of clear fluid (cases 1 and 2). Alternatively, the CSF effusion may remain undiagnosed until meningitis develops as a result of retrograde infection through the defect in the otic capsule (cases 1 and 3).

In addition to the patients described herein, 39 other patients with Mondini dysplasia and meningitis have been described[1,2,9-33] (Table). Age has ranged from 2 months to 41 years, with 60% of patients younger than 4 years and 75% younger than 10 years. No sexual predilection occurs. Sixty-seven percent had a unilateral malformation and profound congenital unilateral sensorineural hearing loss. Most had no vestibular symptoms, although formal vestibular testing was rarely performed. All but three patients suffered at least two episodes of meningitis before the correct diagnosis was made, and two patients had 20 episodes of meningitis prior to surgery.[34,35] All patients required surgical procedures to seal the CSF leak; in 30%, multiple procedures were required to correct the problem.

Mondini dysplasia should be suspected with the clinical triad of congenital (often unilateral) profound sensorineural hearing loss, profound peripheral vestibular weakness, and recurrent meningitis. Associated abnormalities such as Klippel-Feil syndrome, Pendred's syndrome, chromosomal trisomy aberrations, and DiGeorge syndrome may be present, although Mondini dysplasia can result from treatment with teratogenic drugs, like thalidomide, or can occur as an isolated finding.

Radiographic studies and brainstem response audiometry confirm the diagnosis. Thin-cut, high-resolution computed tomography is the procedure of choice; if the presence of a CSF leak is questionable, contrast or radioisotope tracer studies may identify the location of the leak. Brain-stem response audiometry should be performed to determine the functional status of the malformed ear.

Surgical intervention is required to avoid further complications. The method of closure of the fistula is dictated by the functional status of the

Patients With Mondini Dysplasia and Meningitis*

Source, y	Site of Lesion	No. of Episodes/ Organism	Age, y/ Sex	Audiometry	Multiple Procedures
Biggers et al,[10] 1973	Stapes footplate	3/pneumococcus	2 mo/M	. . .	. . .
Barcz et al,[11] 1985	Stapes footplate	5/pneumococcus	8 mo/M	NR (L)	. . .
	Stapes footplate	3/not stated	3 y/F	NR (R)	. . .
Bottema,[12] 1975	Oval window	3/pneumococcus	7 yr/F	Profound SNHL (L)	. . .
Carter et al,[13] 1975	Oval window	3/pneumococcus	19 mo/M	NR (R)	2
Clark et al,[37] 1978	Oval window	2/not stated	13 y/M	Profound SNHL (R)	3
	Stapes footplate	3/pneumococcus	4 y/F	Profound SNHL (B)	2
Crook,[14] 1967	Stapes footplate	4/not stated	1 y/M	SNHL (R)	5
Desjardins et al,[15] 1982	Stapes footplate	2/pneumococcus	6 mo/M	Profound SNHL (R)	. . .
	Oval window	1/*Haemophilus influenzae*	6 y/M	Profound SNHL (R)	. . .
	Oval window	3/*H influenzae,* pneumococcus	17 y/F	NR (B)	. . .
Elverland and Mair,[16] 1983	Stapes footplate	3/not stated	11 y/M	Profound SNHL (L)	. . .
Farrior and Endicott,[17] 1971	Stapes footplate	4/not stated	15 mo/M	Profound SNHL (B)	. . .
Freeland,[34] 1973	Stapes footplate and round window	20/not stated	7 y/M	Profound SNHL (R)	2
Guindi,[18] 1981	Stapes footplate	6/*H influenzae,* pneumococcus	10 mo/M	Profound SNHL (R)	. . .
Harrington and Birck,[19] 1967	Oval window and geniculate ganglion	5/*H influenzae,* pneumococcus	4 y/F	Profound SNHL (B)	2
Harris,[1] 1978	Oval window	2/pneumococcus	18 mo/M	Profound SNHL (B)	. . .
Hicks et al,[20] 1980	Stapes footplate	3/not stated	4 y/not stated	Profound SNHL	. . .
Hipskind et al,[21] 1976	Stapes footplate	"Multiple"/ pneumococcus	2 y/F	Profound SNHL (R)	. . .
	Stapes footplate	2/pneumococcus	41 y/F	"Deaf-mute"	. . .
Hirakawa et al,[22] 1983	Stapes footplate	6/pneumococcus	16 mo/M	Profound SNHL (R)	. . .
Hirther and Schindler,[23] 1985	Stapes footplate	4/not stated	3 y/M	NR (L)	. . .
	Stapes footplate	5/not stated	1 y/M	NR (B)	. . .
Kaseff et al,[24] 1980	Stapes footplate	2/pneumococcus	3 y/M	SNHL (R)	. . .
Komune et al,[25] 1986	Stapes footplate	3/*H influenzae,* pneumococcus	7 y/F	NR (B)	. . .
Mafee et al,[26] 1984	Not reported	"Several"/ pneumococcus	20 y/F	NR (B)	. . .
Manning and Gudrun,[27] 1983	Oval window	4/pneumococcus	20 mo/F	SNHL (B)	. . .
McNab Jones and Fairburn,[28] 1977	Stapes footplate	2/pneumococcus	2 y/M	Profound SNHL (R)	. . .
Mitchell and Ruben,[38] 1985	Stapes footplate and round window	2/not stated	13 y/F	NR (R)	2
Neely,[2] 1985	Stapes footplate and round window	1/pneumococcus	1 y/M	NR (R)	. . .
	Stapes footplate	3/*H influenzae*	7 y/F	NR (L)	. . .
Park et al,[30] 1982	Round window	3/streptococcus	13 y/F	SNHL (R)	2

(Continued on p 612.)

Patients With Mondini Dysplasia and Meningitis (cont)[*]

Source, y	Site of Lesion	No. of Episodes/ Organism	Age, y/ Sex	Audiometry	Multiple Procedures
	Epitympanum	5/pneumococcus	4 y/M	SNHL (B)	5
Parisier and Birken,[29] 1976	Stapes footplate	2/pneumococcus	12 y/M	NR (L)	...
Schuknecht,[9] 1980	Stapes footplate	3/pneumococcus	1 y/F	...	...
	Stapes footplate	1/pneumococcus	37 y/M	NR (R)	...
Schultz and Stool,[31] 1970	Stapes footplate	2/pneumococcus	27 mo/F	Severe SNHL (B)	...
Stool et al,[35] 1967	Roof of the eustachian tube	20/not stated	17 mo/not stated	NR (R)	3
	Stapes footplate	4/pneumococcus	10 y/M	Profound SNHL (L)	2
Tschiang et al,[32] 1973	Stapes footplate	2/pneumococcus	27 mo/F	NR (L)	...
Vermeersch et al,[33] 1980	Stapes footplate	3/*H influenzae*	29 mo/M	NR (B)	...
Present case 3	Stapes footplate	2/pneumococcus	15 mo/M	Profound SNHL (L)	...

[*] NR indicates no response; L, left ear; R, right ear; SNHL, sensorineural hearing loss; and B, both ears.

ear. If hearing is present, it may be possible to stop the leak with a fascial graft. If a stapedectomy is performed, a stapes gusher may occur and preclude a favorable outcome. When the ear is nonfunctional, the vestibule should be packed with fascia, muscle, or fat, and the oval window corked with bone. Alternatively, the middle ear cavity can be obliterated.[36] If the initial procedure does not effectively seal the CSF leak, repeated surgical procedures become necessary. Occasionally, an intracranial approach is required to pack the meatus of the internal auditory canal or the cochlear aqueduct.[35,37,38]

CONCLUSIONS

The child with a Mondini dysplasia is at risk not only for hearing impairment, but also for recurrent meningitis. The diagnosis of the inner ear abnormality requires thin-cut computed tomographic scanning. Audiometric testing dictates the surgical approach necessary to correct the problem. Hearing preservation would be ideal, but the primary goal of surgery must be to stop the CSF leak.

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The Otolaryngologic Manifestations of Pelizaeus-Merzbacher Disease

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• Pelizaeus-Merzbacher disease is a condition of central nervous system dysmyelination. We describe a familial series in which both otologic and laryngologic abnormalities were present. The diagnosis of this invariably fatal disorder can be made on a clinical and/or pathologic basis. As the otolaryngologic manifestations are often the first to appear, the consulting head and neck surgeon may be essential in the initial diagnosis of this hereditary disease.

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The otolaryngologist—head and neck surgeon is often consulted to evaluate head and neck manifestations of neurologic disease. Such is the case with multiple sclerosis and other conditions that may initially present as an otolaryngologic disability. Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive sudanophilic leukodystrophy in which central nervous system myelin fails to mature. The basis for the defect is a lack of proper myelin formation rather than subsequent demyelination.[1] The clinical course is slowly progressive, ultimately ending in death in the second to third decade of life. The present minimal diagnostic criterion is the observation of rolling, wandering "nystagmus" at age 4 to 6 months, followed by a delay in motor development.[2] Pelizaeus[3] in 1885 and Merzbacher[4] in 1910 each used the clinical and neuropathologic abnormalities of one family to originally characterize this entity. We describe one family with PMD to emphasize the otologic and laryngologic abnormalities that may be used in diagnosing this condition.

REPORT OF CASES

CASE 1.—A white male was born November 20, 1953 after a normal full-term pregnancy (Fig 1, II-A). He received a tracheotomy at age 8 hours for what was described as "laryngeal stridor, probably of neurogenic origin." He was also soon noted to have generalized hypotonia and difficulty in swallowing. The feeding problem necessitated partial feeding by gavage. The tracheotomy tube was removed after approximately 1 month, but had to be replaced within a few days due to laryngeal obstruction. The patient was admitted to a convalescent hospital for definitive care at age 1 year 4 months. At that time, the extremities were noted to be spastic and there were "searching movements of the eyes." Multiple efforts to wean the patient from the tracheotomy tube failed. Laryngoscopy was initially performed at age 2 years 1 month after the child accidentally extubated himself. The trachea collapsed with each respiration, indicating the presence of tracheomalacia. The patient suffered cardiopulmonary arrest on June 9, 1956, and died at age 2 years 6 months of pathologically determined diffuse bronchopneumonia. The postmortem examination revealed extensive and diffuse absence of myelin in nearly all white-matter regions except the subcortical U-fibers (Fig 2).

CASE 2.—The proband in the family was the nephew of patient 1, born June 29, 1985, by repeat cesarean section at 37 weeks' gestational age by date, with Apgar scores of 8 and 8 at 1 and 5 minutes. Polyhydramnios

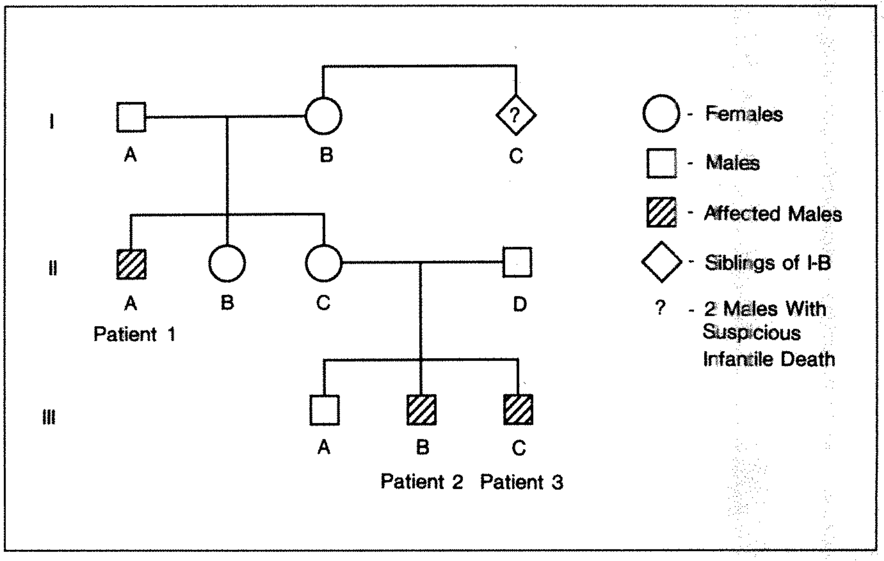

Fig 1.—Genealogy of study family. Maternal great-uncles of patients 2 and 3 are designated by the diamond.

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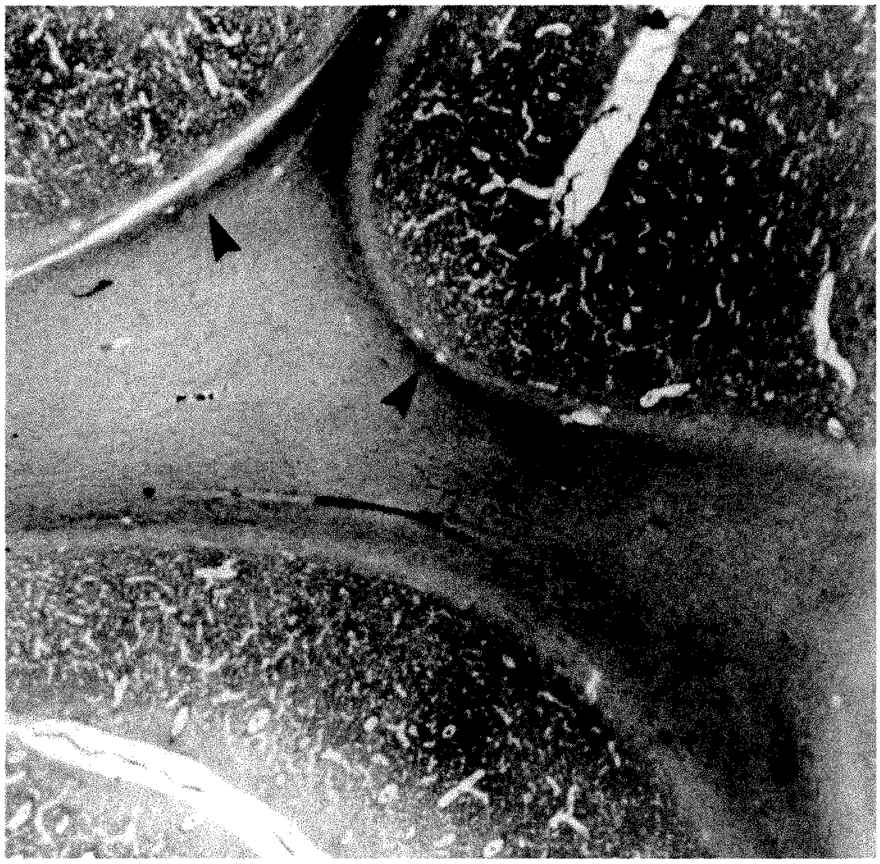
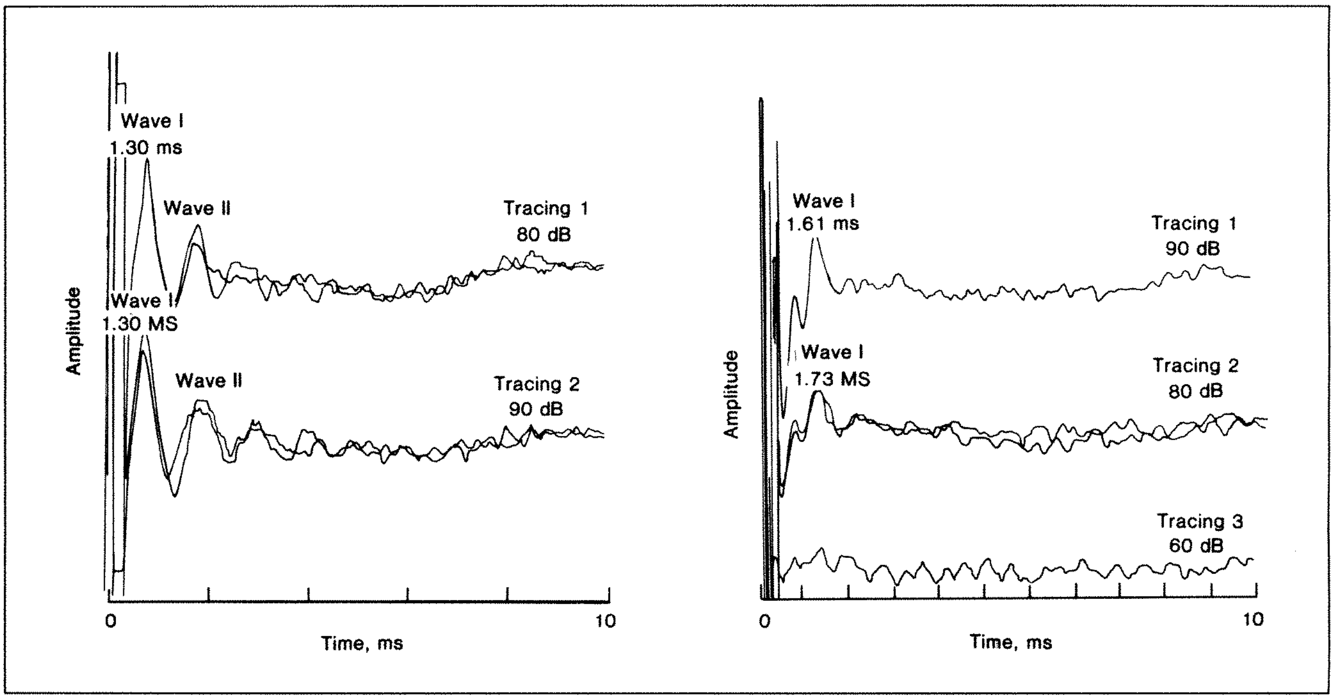


Fig 2.—Histologic preparation of brain specimen from patient 1. Arrowheads indicate myelin, which is limited to the region of the subcortical U-fibers (hematoxylin-eosin, original magnification ×40).

was noted at delivery. The infant had early-onset marked respiratory secretions and upper airway noise. Also noted at that time were marked hypotonia and no suck reflex for the first week. He required frequent suctioning for the first 2 weeks, after which he was noted to have inspiratory stridor. The stridor progressed and the patient developed suprasternal and substernal retractions necessitating otolaryngologic evaluation. Nasolaryngoscopy on September 3, 1985, revealed evidence of vocal cord paralysis with no abduction of the true cords bilaterally. The anatomic structural integrity of the endolarynx was intact. Routine infant screening included an auditory brain-stem response (ABR) performed on July 10, 1985. Responses to a click stimulus (17 per second) at 90 dB HL revealed wave I and wave II only in the right ear and wave I only in the left ear (Fig 3). Wave I latency was 1.30 in the right ear and 1.61 in the left ear. Responses were not present from the rostral brain-stem generators. At examination on October 29, 1985, the patient had developed intermittent nystagmoid eye movements. He subsequently had recurrent episodes of dehydration requiring hospitalization, retarded motor development, decerebrate posturing, and continued rolling eye movements.

Case 3.—The brother of patient 2 was born April 5, 1989, by repeat cesarean section at an estimated gestational age of 39 weeks, and had Apgar scores of 8 and 9 at

Fig 3.—Auditory brain-stem response to clicks (17 per second) in case 2. Peak latencies for wave I in right ear (left) and left ear (right) are indicated.



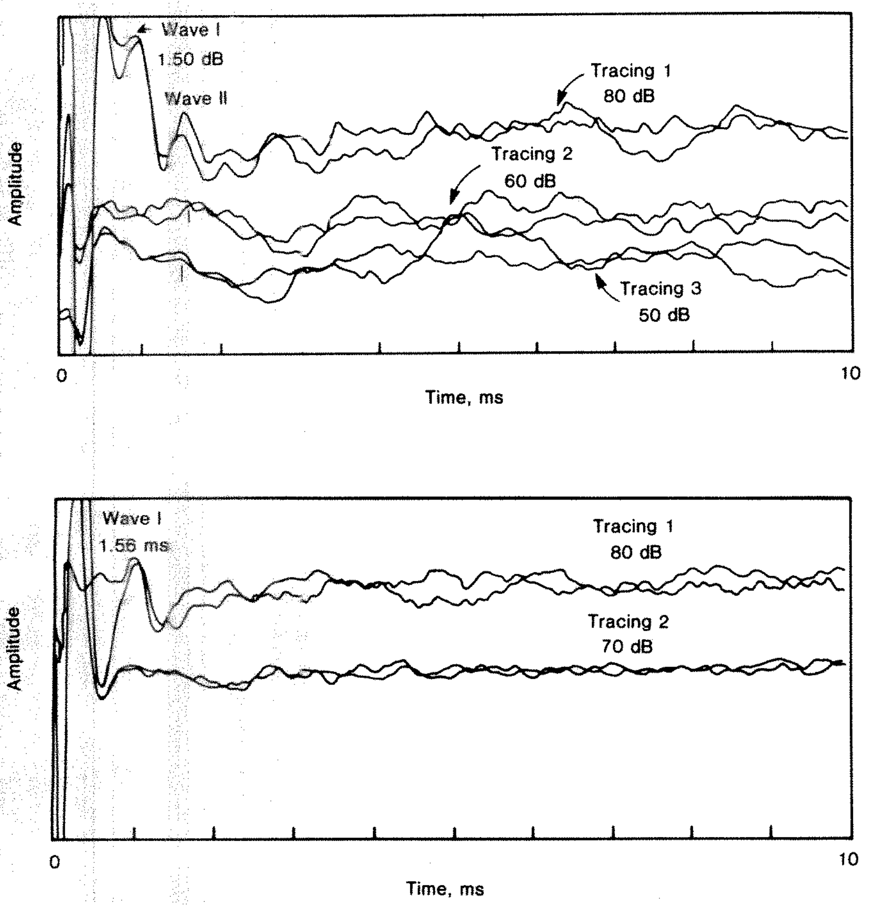


Fig 4.—Auditory brain-stem response to clicks (17 per second) in case 3. Peak latencies for wave I in right ear (top) and left ear (bottom) are indicated.

1 and 5 minutes. The pregnancy was complicated only by polyhydramnios. The infant had postdelivery inspiratory stridor that responded somewhat to positive pressure ventilation and racemic epinephrine administration, but ultimately required intubation. A 3-0 endotracheal tube was the largest that could be passed. Prior to intubation the true cords were noted to move. On examination the child was noted to be hyporeflexic and hypotonic. There was no nystagmus in the first week of life. On the first postnatal day, the infant underwent direct laryngoscopy and bronchoscopy, which revealed a normal lower airway and normal anatomic larynx. However, on lightening of the anesthetic, moderate to severe laryngomalacia with prolapse of both the arytenoids and the epiglottis into the introitus was noted. The vocal cord motion was normal. The patient was extubated postoperatively. Twenty-four hours later he developed apnea and cyanosis that did not resolve with mask ventilation, and thus he was reintubated with a 3-0 tube.

The patient subsequently was extubated but required gavage feedings for dysphagia. Magnetic resonance imaging (MRI) of the brain on the second postnatal day was normal. An ABR to a click stimulus (17 per second) at 80 dB HL demonstrated wave I and wave II only in the right ear and wave I only in the left ear (Fig 4). Wave I latency was 1.50 in the right ear and 1.56 in the left ear. The patient was subsequently discharged.

COMMENT

Pelizaeus-Merzbacher disease is difficult to diagnose in a timely and effective manner. It is inherited, yet no carrier detection is available.[2] Biochemical abnormalities specific to this condition have not been elucidated[5]; amniocentesis is therefore not useful in fetal detection. Postnatal diagnosis is rare and the average age of detectability is between 1 year and 18 months.[2] This allows uninformed subsequent conception to occur with a 50% risk of recurrence in male offspring and a 50% risk of carrier status in female offspring. The importance of neonatal diagnosis and genetic counseling is obvious.

The manner of diagnosis itself has been a source of controversy. Morphologists have stated that it can only be made on pathologic grounds,[6] confirming the diagnosis by neurochemical analysis of the white matter.[7] Others cite inconsistent neuropathologic findings and diagnose the condition on the basis of a defined mode of inheritance and characteristic clinical picture.[5] Except in the rare instance in which an affected individual dies after birth, pathologic evaluation has limited usefulness in immediate counseling. The pathognomonic clinical signs also are delayed. We submit that neonatal stridor, a specific genealogy, and a characteristic ABR can be used to make a presumptive diagnosis.

When stridor has been reported as a sign in PMD, it develops between birth[7] and age 6 weeks.[1] In our family study the stridor was initially identified between delivery and age 2 weeks. In two additional families in which PMD was diagnosed, patients developed stridor at postpartum days 8 and 24.[5] Patient 2 in the present investigation had laryngeal abductor paralysis as the cause for his stridor. This has been previously described in a patient who developed stridor at postpartum day 2 and had abductor paralysis diagnosed by cinefluorography and laryngoscopy 3 months later.[8] Patient 3 suffered from laryngomalacia, as did a child with presumed PMD with an infolding of the epiglottis noted on laryngoscopy at age 1 year.[9] The early presentation of stridor in a male neonate may initiate an otolaryngologic consultation. The head and neck physician must then take the next logical step and recommend an ABR.

The ABRs of our two tested patients were abnormal. The importance of this aberration is twofold. The findings were made in patient 2 at age 11 days and in patient 3 at age 22 days. Thus, early suspicions can lead to an early diagnosis. These two patients represent the earliest documented abnormalities in ABR testing. Previously, patients with PMD from ages 1 month[10] to 20 years[11] have displayed the characteristic wave form.

The second point of significance is

that this wave form may act as a "fingerprint" for this disorder in the proper genealogic setting. De Meirleir et al[12] studied four patients aged 16 months to 9 years with PMD. In all four ABRs, only waves I and II were normal, with normal wave I latency. This loss of the rostral waves and normal wave I latency as seen in our patients has also been substantiated in other cases of PMD.[10,13]

This latter reference[13] is the only previous description of PMD in the otolaryngologic literature and deals primarily with the vestibular findings in a 15-year-old boy with spastic ataxic diplegia, pyramidal symptoms, optic atrophy, and nystagmus. The diagnosis of PMD was suspected because of a similar disorder in a maternal uncle and maternal great-uncle. The family history thus takes on an important role in suggesting the proper diagnosis. In our lineage (Fig 1), note that two maternal great-uncles died suspiciously as infants, reportedly of problems related to "bad milk," and patient 1 was the maternal uncle of patients 2 and 3. This pattern is typical of X-linked recessive inheritance and should be checked in any pedigree of a supposed patient with PMD or female carrier.

The electronystagmographic abnormalities of the aforementioned 15-year-old boy were of the central type. More specifically, the patient exhibited failure of fixation suppression, poor smooth pursuit, and impaired performance of optokinetic nystagmus at high stripe speeds. Electronystagmography during caloric stimulation revealed a very prolonged slow-phase nystagmus with wide eye excursions.[13] A 17-year-old boy[14] with a diagnosis of PMD likewise revealed prolonged slow-phase duration during rotation and caloric stimulation. Thus, while the ABR indicates myelination abnormalities of the rostral brain stem, and laryngeal abnormalities may suggest defects in the upper motor neurons and upper brain stem, the electronystagmography points to involvement of the brain-stem-cerebellar connections. The utility of electronystagmography in the early diagnosis of PMD cannot be determined by its reported use in these two adolescent cases. Further investigation with infants is needed.

The radiologic evaluation of PMD has been recently revived with the advent of MRI. Previously, computed tomographic scans have been of little help in the diagnosis of this disease, yielding negative results or abnormalities only at an advanced stage of the disease.[15] Magnetic resonance imaging has been reported to be useful in reflecting histologic myelination changes[16] and even in identifying female carriers of the disease.[17] One author cautions, however, that although the MRI findings may correlate well with the pathology of the disease, they are by no means specific for it.[18] In this study, MRI examinations of two patients revealed consistent abnormalities. T_1-weighted images revealed cerebral atrophy and low brain volume, and T_2 images demonstrated reversal of the normal gray/white matter signal relationships, with white matter represented by higher signal intensity than the surrounding gray matter. The ages of these two patients at the time of MRI evaluation were 15 and 18 years. As previously stated, patient 3 in our study had a normal MRI evaluation at age 2 days. This may easily be explained by the lack of sufficient dysmyelination at this stage of the disease and by differences in forms of PMD.[16] Magnetic resonance imaging may be considered another confirmatory piece of clinical evidence in the diagnosis of PMD.

CONCLUSION

Pelizaeus-Merzbacher disease is an X-linked recessive inheritable neurologic disorder that ultimately ends in premature death of afflicted males. Female carriers of the disease may unknowingly propagate the disease to subsequent generations. Early diagnosis enables the parents to plan future births appropriately. Therefore, those diagnostic modalities and clinical signs that manifest early are of prime importance. Optic atrophy, mental retardation, pyramidal syndrome, and dystonia all occur primarily in early childhood.[5] Nystagmus, stridor, and abnormal ABR usually develop in the first 6 months. The otolaryngologist–head and neck surgeon is essential in the timely diagnosis of this catastrophic central nervous system disease.

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The Diagnostic Dilemma of Otosyphilis

A New Western Blot Assay

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• **Currently, the diagnosis of otosyphilis applies to any patient with otologic symptoms of unknown cause and a positive fluorescent treponemal antibody–absorption (FTA-ABS) test result. However, the FTA-ABS assay can have false-positive results and does not distinguish between active and treated disease. The VDRL test, which has been used to distinguish inactive disease, frequently yields negative results in patients who are nonetheless given the diagnosis of otosyphilis. A new Western blot assay can eliminate the possibility of a false-positive result and can confirm whether the infection is active. This assay was used to diagnose unsuspected active syphilis in a patient believed to have autoimmune ear disease. In three other cases of suspected otosyphilis, the diagnosis was refuted when the Western blot demonstrated that the FTA-ABS result was false-positive or that the infection was inactive.**

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Syphilis is often considered in the differential diagnosis of sudden-onset sensorineural hearing loss, and both congenital and acquired forms of the infection have been implicated.[1-8] No single laboratory test is universally accepted as the "gold standard" by which the diagnosis of luetic ear disease can be confirmed. VDRL reactivity has a high false-positive rate among patients with collagen-vascular diseases. Serum fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination assay-*Treponema pallidum* (MHA-TP) assays are more specific but cannot discriminate between active and treated disease. We describe a patient with two episodes of sudden-onset sensorineural hearing loss that were believed to have an autoimmune cause. Previous physicians who cared for this patient considered her reactivity in the FTA-ABS assay to be a manifestation of a collagen-vascular disorder. However, by means of a new Western blot assay for serum and cerebrospinal fluid (CSF) antibodies to *T pallidum*, we were able to confirm active syphilis. We are now inclined to consider her ill-defined arthritis, anemia, positive test results for immune complexes, and sensorineural hearing loss as manifestations of syphilis. We report this and three other potentially ambiguous cases to illustrate the usefulness of new technologies that are being developed for the diagnosis of syphilis and to discuss the difficulties in confirming the diagnosis of otosyphilis.

REPORT OF CASES

CASE 1.—A 43-year-old woman suffered sudden-onset, unilateral hearing loss that had not resolved despite 2 months of corticosteroid therapy. Four months earlier, she had experienced vertigo and sudden hearing loss in the opposite ear, but had regained her hearing after 3 days of high-dose steroid therapy. A positive serum FTA-ABS result had been found during the evaluation of her second episode of hearing loss. Several factors led her physicians to believe that this was a false-positive result. Her exemplary social situation and life-style made the possibility of sexually transmitted diseases inconceivable. She reported that at the time of obtaining her marriage license, she had a positive syphilis test result which she was told was false-positive. Moreover, she had several signs and symptoms of collagen vascular disease. Two years earlier, she had developed anemia, fusiform changes of her proximal interphalangeal joints, and mottling of the skin over her ankles and feet. Test results were positive for cryofibrinogens and marginally positive for antinuclear antibodies; C4 levels were decreased. She was considered to have an atypical vasculitis with anemia of chronic disease. Prednisone therapy (60 mg/d) resulted in resolution of her arthritis and anemia. At the time of her second hearing loss, C4 levels were still low, and the conglutinin slide phase assay for im-

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mune complexes was 150 aggregated human globulin equivalents per milliliter (AHG Eq/mL) (normal, <5 AHG Eq/mL). The cause of her hearing loss was believed to be autoimmune.

On evaluation, audiometric studies confirmed a profound left-sided sensorineural loss. Results of oculomotor testing were within normal limits, but a 47% left-sided weakness was detected by caloric testing. Computed tomographic and magnetic resonance imaging scans of the temporal bones revealed no abnormalities. Erythrocyte sedimentation rate and results of thyroid function studies, complete blood cell count, and lipoprotein electrophoresis were normal. Results of serologic tests for rheumatoid factor, cryoglobulins, and antinuclear antibodies were negative. Serum IgG, IgM, and IgA levels were normal without oligoclonal bands. Serum C3 was low-normal at 0.79 g/L (normal, 0.75 to 1.5g/L) and C4 was 0.08 g/L (normal, 0.13 to 0.35 g/L). The C1q binding assay for immune complexes was negative. The Raji immune complex assay detected greater than 1000 μg AHG Eq/mL (normal, <12 μg AHG Eq/mL).

The serum FTA-ABS result was positive but VDRL and MHA-TP tests were nonreactive. Results of serologic tests for human immunodeficiency virus were negative. A diagnosis of neurosyphilis was considered but the patient's CSF contained normal levels of protein and glucose and no cells. VDRL and FTA-ABS tests of the CSF were both nonreactive. High-resolution electrophoresis of the CSF revealed no oligoclonal bands.

Case 2.—The second patient was a 75-year-old man who complained of lightheadedness when arising from a reclining position. He had arteriosclerotic heart disease and insulin-dependent diabetes. He had noted a slight hearing loss but no tinnitus. The results of his physical examination were essentially normal. Audiometric studies showed a mild right-sided low-frequency sensorineural loss and 40- to 45-dB losses for high frequencies in both ears. Results of oculomotor testing were within normal limits but a 63% left-sided weakness was detected by caloric testing. Computed tomographic scans revealed no abnormalities of the temporal bones. The erythrocyte sedimentation rate was elevated at 35 mm/h. A complete blood cell count showed a mild anemia. Thyroid function test results were normal but triglyceride levels were mildly elevated. Serum IgG and IgM levels were normal without oligoclonal bands. C3 and C4 levels were normal and the result of a C1q binding test for immune complexes was negative. Results of serologic tests for rheumatoid factor and antinuclear antibodies were negative. A serum FTA-ABS result was positive. The patient stated that he had been treated for syphilis approximately 10 and 40 years earlier.

Case 3.—A 39-year-old man complained of fluctuating tinnitus, hearing loss, and aural pressure during the preceding month. He had a 42-dB flat right-sided sensorineural loss and a 39% right-sided weakness detected by electronystagmography. Summating potentials were not elevated. A computed tomographic scan of the temporal bones was normal. Complete blood cell count and triglyceride levels were normal. A serum FTA-ABS was marginally reactive on two occasions, although the patient denied being at risk for sexually transmitted diseases.

Case 4.—At age 12 years, this man had received intramuscular streptomycin for hematuria and topical quinine for tonsillitis. He first noted decreased hearing and tinnitus at age 19 years. When initially evaluated at age 32 years he had normal acuity below 500 Hz, dropping to a profound loss above 1000 Hz in both ears. Tomograms of the internal auditory canals were normal. Results of serum protein and lipoprotein electrophoreses were normal. A serum FTA-ABS result was positive and was confirmed by a second laboratory. A VDRL performed by the Regional State Health Department Laboratory was negative. The patient denied any activity that might have led to exposure to syphilis but agreed to receive a full course of antibiotic therapy and a trial of corticosteroids. However, a friend of the patient described to him in graphic terms the potential side effects of corticosteroids and the patient elected to terminate the treatment after only a few days. The otologist was not sufficiently sure of the diagnosis of otosyphilis to justify encouraging the patient to continue with corticosteroid therapy.

MATERIALS AND METHODS

Serum and CSF were analyzed by an electrophoretic transfer blotting (Western blot) technique for the presence of antibodies specific for antigens extracted from *T pallidum*.[9,10] Briefly, solubilized treponemal proteins were separated according to relative molecular size by electrophoresis through a polyacrylamide gel and transferred onto nitrocellulose paper. Strips of paper containing a cross-section of the fractionated treponemal proteins were incubated with dilutions of serum or CSF, allowing specific antibodies to bind to the antigen. Bound antibodies were identified by peroxidase-conjugated animal antisera to human immunoglobulins followed by an enzyme-mediated colorimetric reaction. Human antibodies specific for treponemal antigens were seen as dark bands located at distances along the paper strip that correlated with the known migration distances of treponemal antigens of specific molecular weights. A reference serum sample, pooled from patients known to have secondary syphilis, was diluted and included in all experiments as a positive control.

RESULTS

Patient 1's serum contained antibodies specific for multiple antigens of *T pallidum* (Fig 1). The presence of both IgG (lanes G through J) and IgM (lanes B through E) antibodies indicated an active, ongoing infection. The pattern was essentially identical to that seen in the positive control serum (lanes A and F). Antibodies could be found in this patient's serum even when diluted to 1:400 (lanes E and J). Specific IgM and IgG antibodies to *T pallidum* were also found in the CSF (Fig 2), even when extensively diluted.

Serum from patient 2 contained only antitreponemal antibodies of the IgG class (Fig 3; lane D). There were essentially no antitreponemal antibodies of the IgM isotype (lane C), indicating that the infection was not active and no further antibiotic treatment was indicated.

Serum from patient 3 (Fig 4) contained tiny amounts of IgM (lane C) and IgG (lane D) antibodies that reacted with flagellar antigens in the 30- to 45-kd range. The bands were very faint, indicating that the antibodies were present in very low concentrations compared with the positive control serum (lane B). Furthermore, no more than five antigens were recognized, compared with over 20 antigens recognized in the positive control serum. Results from patient 4 were the same as from patient 3 and are not shown. A few very faint bands were seen in the region of the 30- to 45-kd flagellar antigens only. Thus, both of these patients can be confirmed as having false-positive FTA-ABS results and the diagnosis of otosyphilis is disproved.

COMMENT

Treponema pallidum cannot be grown in vitro; only during the first few weeks, when the spirochete can be recovered from the chancre, can syphilis be diagnosed by direct identifica-

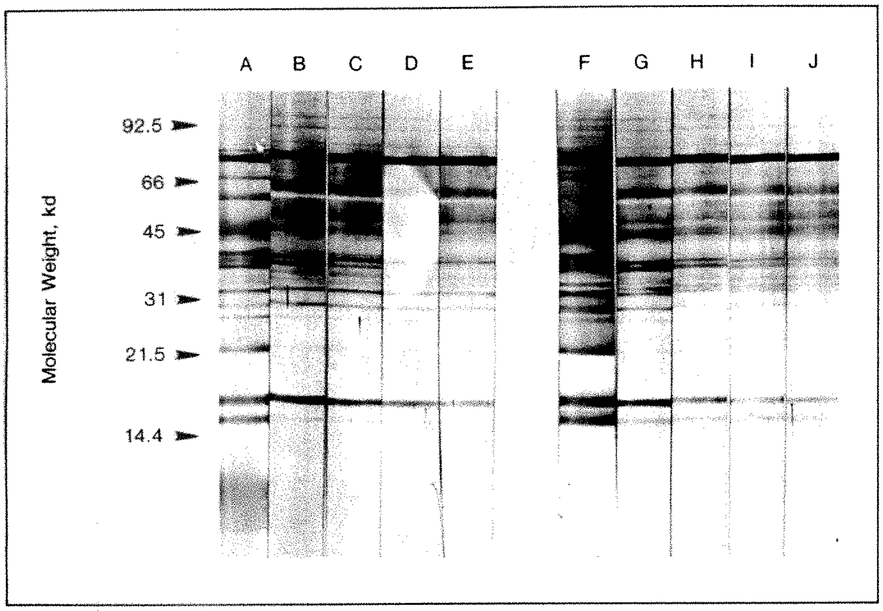

Fig 1.—Lanes A through E were developed for IgM antibodies and lanes F through J were developed for IgG antibodies. Lanes A and F contain a positive control syphilitic serum pool diluted to 1:100. The first patient's serum was tested in serial dilutions: lanes B and G, 1:50; lanes C and H, 1:100; lanes D and I, 1:200; and lanes E and J, 1:400. Migration distances of known molecular weight markers are indicated along the left margin.

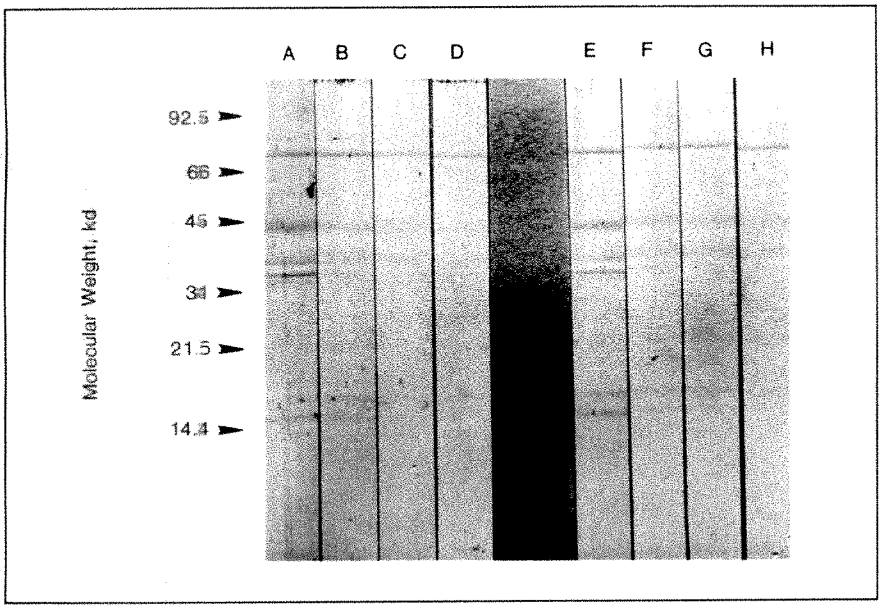

Fig 2.—Lanes A through D were developed for IgM antibodies and lanes E through H were developed for IgG antibodies. The first patient's cerebrospinal fluid was tested in serial dilutions: lanes A and E, 1:25; lanes B and F, 1:50; lanes C and G, 1:100; and lanes D and H, 1:200. Migration distances of known molecular weight markers are indicated along the left margin.

tion of the infecting organism. Thereafter, the diagnosis is determined by serologic tests that measure the host humoral immune response to the spirochete. VDRL and rapid plasma reagin are nontreponemal tests that rely on the presence of antibodies that cross-react with antigens expressed on bovine heart cardiolipin. These tests usually become nonreactive 6 to 12 months after appropriate treatment. Patients with systemic lupus erythematosus or other collagen-vascular diseases may have persistently false-positive test results. It is believed that antibodies cross-reactive with cardiolipin are coincidentally produced during the unregulated immune responses characteristic of these conditions.

Treponemal-specific assays such as FTA-ABS or MHA-TP are more sensitive and more specific, but may remain positive for life despite adequate treatment. Our first patient had a positive FTA-ABS result and negative MHA-TP and VDRL results. The inconsistencies in these results were resolved by detection of serum antibodies specific for *T pallidum* with a Western blot test and illustrate the need for more precise assays. The presence of a single antibody population that is cross-reactive with *T pallidum* can be sufficient to produce a positive FTA-ABS result. When assayed by the Western blot technique, such serum might contain faint reactivity to only a few antigens from *T pallidum*, typically the 30- to 45-kd flagellar antigens (case 3, Fig 4, and case 4). However, for confirmation of syphilis by the Western blot assay, one must see multiple antibody populations, each reacting with a different antigen characteristic of *T pallidum.* The multiple antibodies found in the first two patients' serum samples and the reference positive control serum illustrate the polyclonality of the typical antitreponemal response.

Unlike all previous assays, the Western blot approach identifies the antibody isotype, indicating whether or not the infection is active. Patients with primary and secondary syphilis have both IgM and IgG antibodies to *T pallidum.*[9] After successful treatment, only IgG antibodies persist in the circulation. Our first patient had IgM antibodies, indicating an active infection. It has not been possible to determine how her infection was acquired. She had received 2 U of packed red blood cells for treatment of anemia 2 years earlier, but this is an unlikely vector. Her mother had been said to have a "false-positive" test for syphilis and her father died of a degenerating neurologic disease. Thus, it was conceivable that her infection was acquired congenitally. However, serum from her mother was subsequently tested

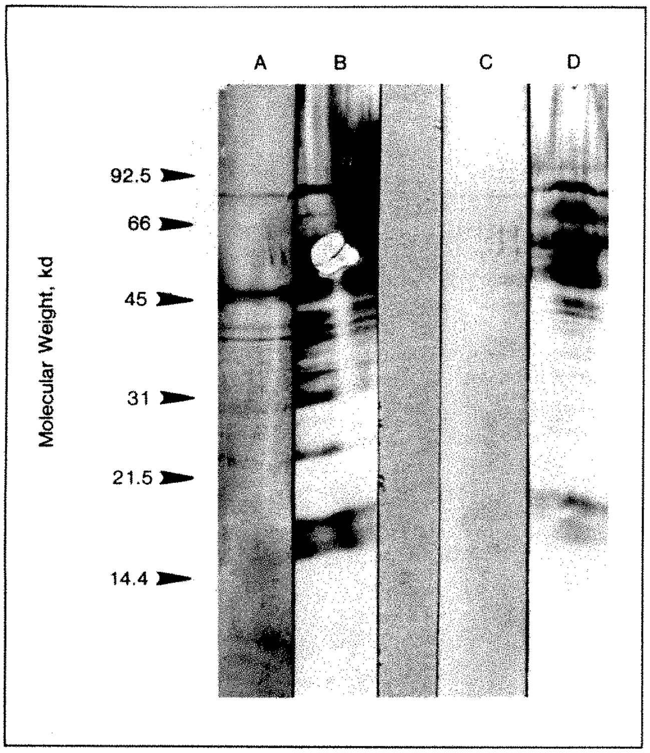

Fig 3.—Lane A contains molecular weight reference markers. Lane B contains the positive control syphilitic serum pool diluted to 1:100 and developed for IgG antibodies (IgM antibodies have an identical pattern). The second patient's serum was tested for IgM antibodies (lane C) and IgG antibodies (lane D) at a 1:100 dilution.

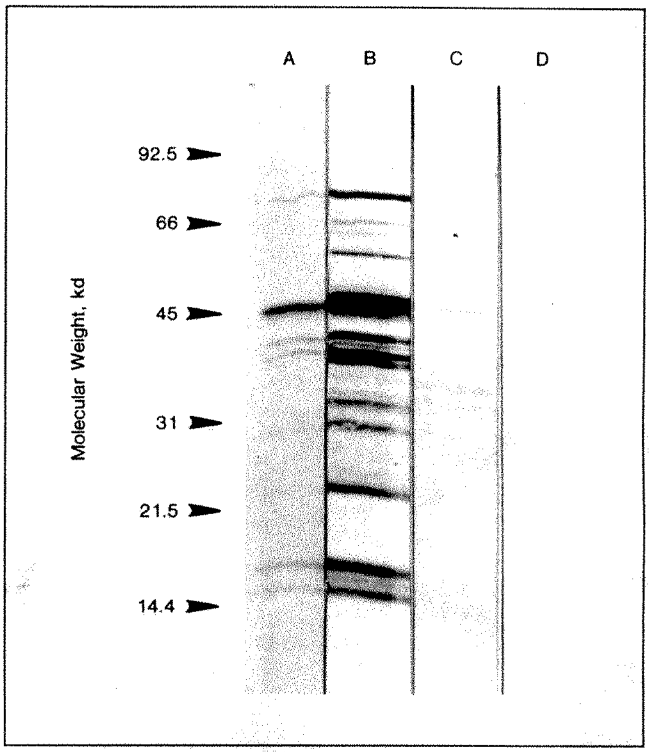

Fig 4.—Lane A contains molecular weight reference markers. Lane B contains the positive control syphilitic serum pool diluted to 1:100 and developed for IgG antibodies (IgM antibodies have an identical pattern). The third patient's serum was tested for IgM antibodies (lane C) and IgG antibodies (lane D) at a 1:100 dilution.

and showed no evidence of any syphilitic infection, either active or treated.

What is otosyphilis? There is no characteristic clinical presentation; hearing loss has been described as typically unilateral, bilateral, progressive, sudden, fluctuating, with abnormal or normal discrimination scores, and with or without vertigo.[1-8,11,12] Patients' otologic symptoms have been attributed to congenital or latent syphilis, yet they may have no evidence of active infection. Most patients have other symptoms or stigmata, although monosymptomatic disease has been described for both congenital and acquired syphilis.[1] The diagnostic criteria offered by most authors are (1) a positive FTA-ABS result and (2) the absence of other identifiable causes.[1-3,7,8,11] In many if not the majority of cases cited, the VDRL result is negative. Did these patients really have active syphilis? Although the VDRL result may become negative in advanced disease, prior to the Western blot assay the VDRL assay was the only test that indicated whether the syphilis infection was active.

Does otosyphilis exist? Some supporting data can be gleaned from epidemiologic studies. Two large surveys have found an increased incidence of positive serologic test results in patients with hearing loss, although neither study is truly randomized. Zoller et al[8] found positive FTA-ABS results in 20 of 306 patients with sensorineural hearing loss of unknown cause as opposed to 2 of 100 controls. Hughes and Rutherford[2] selected over 400 "high-risk" patients for serologic testing from 5439 patients with otologic symptoms. Thirty-seven had a reactive FTA-ABS result compared with 2 of 100 controls with presbycusis. The results in both of the control patients were dismissed as false-positive, whereas all positive results in the experimental group were assumed to be true-positive "by definition" to avoid underestimating the incidence of syphilis-associated ear disease. No justification is given for this investigational "double standard." An alternative approach is to ask whether patients with syphilis have an increased frequency of hearing loss. Tamari reported abnormal audiometrics in 17% to 29% of patients with late congenital, latent, or asymptomatic neurosyphilis increasing to 78% to 84% of those with tabes or paresis.[1] In another study, 7 of 26 patients with secondary or early latent syphilis had abnormal auditory brain-stem reflexes and one half had high-frequency hearing loss.[13] Not included in these studies were patients with syphilitic meningitis who had a higher incidence of hearing loss as well as involvement of other cranial nerves.

How can the diagnosis of otosyphilis be confirmed? Postmortem examinations of the temporal bones from patients with advanced syphilis reveal an obliterative endarteritis, osteitis of the otic capsule, damage to the organ of Corti, dilation of the cochlear duct, cellular infiltrate, and occasional endolymphatic hydrops.[4] However, short of an autopsy, there is no way to definitively implicate *T pallidum* in ear disease, and there is a particular dilemma in applying the diagnosis to a patient who has no evidence of active infection. The quandary is neatly summarized by Becker[1]: "1) Does this patient have syphilis? 2) Is syphilis causing the cochleovestibular dysfunction?" In the patient with syphilitic meningitis, examination of the CSF will reveal elevated protein levels and a lymphocytosis. However, a distinction is made between neurosyphilis and otosyphilis. Evidence of central nervous system inflammation is not required for the latter diagnosis, and indeed is often absent. Perilymph is considered to be distinct from CSF and it is postulated that inflammation of the otic capsule will not necessarily extend to the central nervous system. Our first patient's normal CSF protein level and absence of pleocytosis suggest that she did not have classic neurosyphilis. However, her CSF contained antibodies specific for *T pallidum*, which might have been locally produced or represent serum antibodies that diffused into the CSF. The FTA-ABS assays of CSF are open to question and VDRL assay results are often negative in patients with presumed otosyphilis. With the increased sensitivity of the Western blot assay, we may find that examination of the CSF will offer new diagnostic information in the elucidation of luetic otitis.

If spirochetes infect cells in or near the inner ear, there may be direct damage. An exuberant immune response to the organisms may extend the zone of injury to involve adjacent uninfected tissues, giving the external appearance of an autoimmune process. Steroids, the mainstay treatment of autoimmune disorders, may also lead to improvement when combined with antibiotics in the treatment of syphilis-associated hearing loss.[1-3,6,7,11,12] In light of their shared hypothetical pathophysiology, it is not unexpected that syphilitic and autoimmune-mediated ear disease would be difficult to distinguish. Our first patient's presumed autoimmune disease process can be explained equally well by the diagnosis of syphilis. Her previous arthritis and anemia could have been results of syphilis. She lacked many of the features commonly associated with autoimmunity, such as an elevated erythrocyte sedimentation rate and the presence of rheumatoid factors and antinuclear antibodies. She had a persistently decreased C4 level and positive Raji and conglutinin assay results for circulating immune complexes. Patients with syphilis frequently have circulating immune complexes that may contain both treponemal and endogenous host antigens.[14]

The otologist who successfully diagnoses syphilis may be unable to improve the patient's otologic symptoms with a course of antibiotics and steroids. Response rates vary from 10% to 75% and are often transient.[1-3,6,7,11,12] However, treatment may avert later more serious neurologic or cardiovascular sequelae. The Western blot assay allows physicians to distinguish between active and treated disease as well as to identify atypical or subtle presentations of the disease. With further study, we may eventually be able to fulfill Koch's postulates and define the relationship between *T pallidum* and sensorineural hearing loss more precisely.

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Resident's Page

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University of Virginia School of Medicine, Charlottesville

PATHOLOGIC QUIZ CASE 1

Roy R. Casiano, MD; Scott H. Goldberg, MD; Robert Strimling, Miami, Fla

A 58-year-old white woman presented with a 1-year history of dysphagia caused by solid foods. She denied odynophagia, otalgia, or respiratory difficulties. Physical examination revealed lateral oropharyngeal fullness projecting submucosally toward the midline and protruding into the hypopharynx, below the level of the epiglottis. The larynx was uninvolved, with normal mobility and laryngeal crepitation. Findings of the remainder of the examination were normal.

With the patient under general anesthesia, the mass was excised using a neck approach. The lesion measured 3.0 cm in diameter. Sections of the lesion are shown in Figs 1 and 2.

What is your diagnosis?

PATHOLOGIC QUIZ CASE 2

Roy R. Casiano, MD; Christian L. Otrakji, MD; Robert Strimling, Miami, Fla

A 71-year-old white woman was referred to Jackson Memorial Hospital, Miami, Fla, with a 2-year history of intermittent pains in her right temporal area and a 2-month history of a progressively enlarging nontender neck mass in the area of the right mandibular angle. Her surgical history was significant for a wide local excision and radical lymphadenectomy in the left side of the groin for a superficial spreading melanoma of the left leg 7 years earlier. The patient had no other complaints.

Physical examination revealed a 3 × 1-cm firm, submucosal, ill-defined mass in the right lateral aspect of the pharyngeal wall. The findings of the neck examination were remarkable for a fullness at the angle of the mandible on the right. There was no other lymphadenopathy noted in the head and neck region. Findings of the nasal examination were normal. The results of the rest of the examination of the head and neck, including cranial nerves and salivary flow, were within normal limits. No other suspicious skin or mucosal lesions or lymphadenopathy was found elsewhere in the body. Roentgenography of the chest and a liver profile showed no abnormalities.

Computed tomography revealed a heterogeneously enhancing mass with its epicenter in the right parapharyngeal space. The mass extended from just below the level of the nasopharynx to the angle of the mandible on the right, possibly arising from the deep lobe of the parotid gland. A computed tomographic scan of the paranasal sinuses was normal. Because involvement of major blood vessels could not be totally excluded, magnetic resonance imaging was performed. T_1-weighted images revealed an isodense right parapharyngeal mass with ill-defined borders. The right external carotid artery was noted to be coursing through the tumor's anterior aspect. Fine-needle aspiration was performed (Fig 1).

The patient underwent surgical excision of the mass through a modified Blair incision. With lateral mandibular retraction and blunt dissection medial to the mandible, the tumor was easily exposed and resected. It was well encapsulated within the parapharyngeal space, and encased the external carotid system.

What is your diagnosis?

PATHOLOGIC QUIZ CASE 1

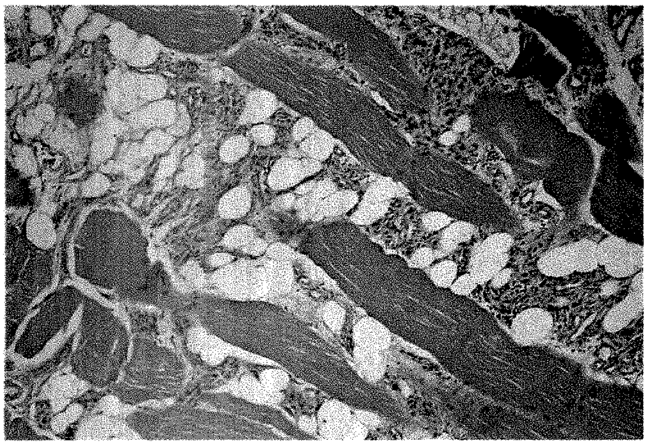

Figure 1.

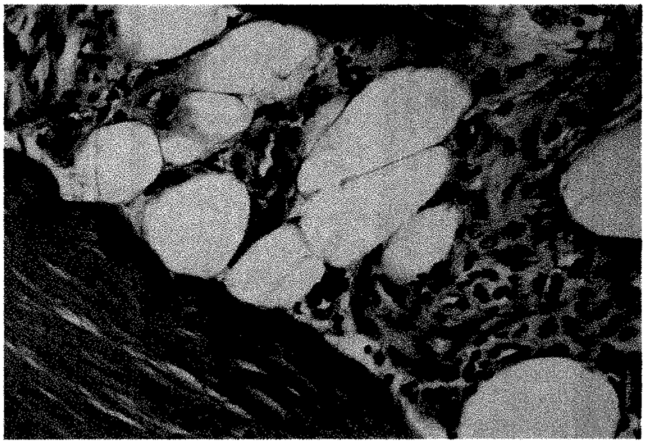

Figure 2.

PATHOLOGIC QUIZ CASE 2

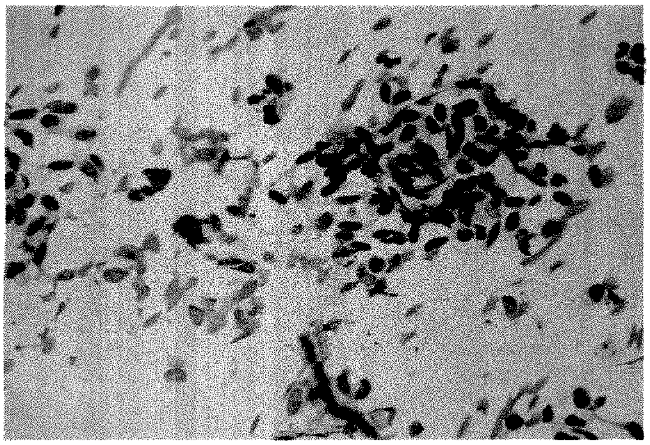

Figure 1.

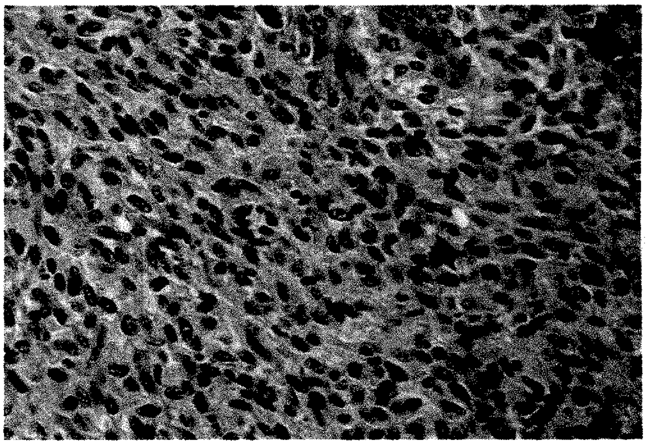

Figure 2.

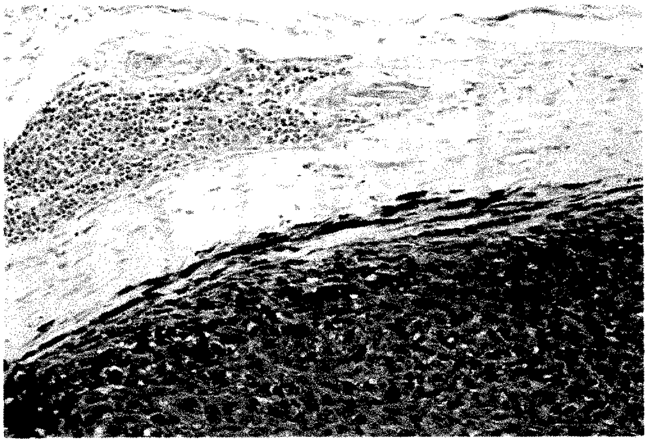

Figure 3.

Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 1

Pathologic Diagnosis: Intramuscular angiolipoma.

Angiolipomas are benign tumors composed of varying degrees of maturing lipomatous and vascular tissue.[1] They were first mentioned in the English literature in 1912 by Bowen, who described a young patient with multiple discrete subcutaneous tumors that met clinical and histopathologic diagnostic criteria.[2]

Angiolipomas represent 5% to 17% of all lipomas. In general, they are found in a younger population (≤ 30 years of age). Grossly, angiolipomas feel rubbery and slightly firmer than a lipoma. They are yellow to red and may or may not be encapsulated, depending on the specific type.

Angiolipomas may be subclassified into the following two distinct types based on clinical and histopathologic differences: infiltrating and noninfiltrating. Noninfiltrating angiolipomas are much more common and represent the type described by Bowen.

Noninfiltrating angiolipoma, also referred to as circumscribed angiolipoma, presents as a subcutaneous nodule, or more commonly as multiple subcutaneous nodules that rarely exceed 4 cm in diameter. Multiple tumors are present in 80% of patients, and a family history is also sometimes noted. They occur almost exclusively during or after puberty (average age at onset, 21 years). The upper extremities are the most common tumor location, and the chief complaint is usually dull pain or tenderness to touch, or an uneasy sensation. The pain is directly related to the amount of vascularity within the tumor.

Histologically, there is a variable ratio of mature adipose to proliferating capillaries, arranged haphazardly.[3] A dense connective tissue capsule with fibrous septa is evident, often in association with the vascular component of the tumor. The vascular component may contain erythrocytes or microthrombi. No atypia, pleomorphism, or mitotic figures are present. Management consists of enucleation, and recurrence is rare.

The infiltrating variety is much rarer, representing less than 10% of angiolipomas. The tumors arise in deep soft tissue and are usually solitary. A family history of this type of tumor or an association with noninfiltrating angiolipomas is rare. Infiltrating angiolipomas occur in all age groups, but are more common in a younger population (mean age at initial presentation, 35.5 years).[4] Lower extremities are the most common site, followed by the lower part of the neck and the shoulders. Angiolipomas of the parapharyngeal space, in general, are rare tumors.[5] Grossly, these tumors have ill-defined borders and are nonencapsulated or partially encapsulated. Histologically, these tumors are also composed of mature lipocytes with delicate, proliferating, haphazardly arranged blood vessels. However, infiltrating angiolipomas are characterized by invasion of surrounding skeletal muscle and fibrocollagenous tissues.

Management of the infiltrating angiolipoma includes wide surgical excision with close follow-up. The local recurrence rate may be as high as 50%. Local recurrences are managed with radiotherapy if resection is incomplete.[2]

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Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 2

Pathologic Diagnosis: Malignant melanoma.

Malignant melanoma is defined as a malignant neoplasm of melanocytes. Histologically, malignant melanoma is characterized by a proliferation of large polygonal cells with abundant cytoplasm. Mitotic figures and pleomorphism are usually present. The tumor cells typically cluster in nests, although not in this particular case. The nuclei contain prominent nucleoli and pseudoinclusions representing entrapped cytoplasm resulting from sectioning through nuclear membrane invaginations. Melanin, which is found in about half the cases of malignant melanoma, is diagnostic (Fig 2). However, on standard hematoxylin-eosin staining, it can sometimes be confused with iron deposition secondary to bleeding within a tumor. Specific stains for melanin (Fontana-Masson stain) and iron (iron stain) can clarify this issue. When melanin is absent, the tumor is called an amelanotic malignant melanoma. Melanomas may demonstrate one or more of three cell types: epithelioid, spindle, and small cell. This particular case exhibited all three. Epithelioid cells are large, approximately 15 to 20 μm in diameter, with large nuclei, prominent nucleoli, and abundant dusty, tan cytoplasm. Spindle cells are characteristically elongated and fibroblastlike in appearance. The less common small-cell type, also called nevuslike melanoma cells, is roughly 6 to 10 μm in width, with large nuclei, scant cytoplasm, and little or no melanin. These cells are usually the most difficult to recognize. Sometimes, they are found in small groups of three to five, creating a somewhat whorled pattern.[1] In the absence of melanin, immunohistochemical stains, including S100 protein and melanoma antigen stains, can prove helpful. A strongly positive S100 stain confirmed this diagnosis (Fig 3).

The pathologic differential diagnosis of melanoma can be easily confused with other entities, especially on fine-needle aspiration. On fine-needle aspiration, malignant melanoma characteristically demonstrates a single-cell pattern as opposed to forming sheets of cells, as in carcinomas. Nonetheless, lacking melanin, the fine-needle aspirate in this particular case was interpreted as poorly differentiated or undifferentiated tumor, without further subclassification (Fig 1). Batsakis et al[2] noted that melanomas may be confused with a number of other tumors, including undifferentiated carcinoma, lymphoma, and rhabdomyosarcoma. A diagnosis of an undifferentiated neoplasm in a patient with a history of malignant melanoma should strongly suggest metastatic disease.

Also, although computed tomography and magnetic resonance imaging are undoubtedly invaluable to the surgeon for preoperative anatomical delineation, metastatic melanoma may also be confused with other more frequent parapharyngeal lesions. A well-encapsulated lesion with heterogeneous enhancement may well be a salivary gland tumor or metastatic carcinoma. Work and Hybels[3] found that 48% of all parapharyngeal tumors in their series were benign or malignant salivary gland tumors. The remainder were neurogenic tumors (32%), vascular tumors (5%), lymphomas (2.5%), and miscellaneous lesions (12.5%). Other authors have reported similar findings.[4]

Primary malignant melanoma involving the head and neck is most frequently seen as a cutaneous lesion with or without regional lymphadenopathy.[5] In descending order of frequency, the face, the neck, and the scalp are the most common head and neck sites.[2,6] Primary mucosal melanoma of the upper aerodigestive tract is uncommon in the United States and represents only 1.7% to 3.0% of all primary melanomas.[7,8] The most frequent site of primary mucosal melanoma in the upper respiratory tract (excluding the oral cavity) is the nasal cavity, in which 70% of all lesions occur. The paranasal sinuses account for the majority of the remaining cases. In the oral cavity, almost 80% of all primary malignant melanomas occur in the mucosa of the maxilla.[9] The larynx is a rare primary site.[2]

Metastatic malignant melanoma to the head and neck from a distant primary is not unusual. Malignant melanoma is known to seed microscopically to regional and/or distant sites early in its evolution and may require many years until its presentation.[5] Undoubtedly, if the original histologic sections of our patient's primary lower-extremity lesion were available, the histopathologic features would be identical, or at least very similar, to those of the later presenting parapharyngeal metastatic tumor.

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Residents and fellows in otolaryngology are invited to submit quiz cases for this section and to write letters to the ARCHIVES *commenting on cases presented. Quiz cases should follow the patterns established and must be submitted in duplicate. Photomicrographs must be clear and can include an outline drawing with important structures labeled, especially in the case of histopathology of the ear. Illustrations must be submitted as positive color transparencies (35 mm preferred). Do not submit color prints unless accompanied by original transparencies. Transparencies should be carefully packaged in a separate container. Please do not submit glass-mounted transparencies or the actual glass histology slides. Material for the Resident's Page should be mailed to the Chief Editor.*

Reprints not available.

Letters to the Editor

Antibiotics for Secretory Otitis Media

To the Editor.—The recent article by Thomsen and coworkers[1] concludes that antibiotics (amoxicillin with clavulanate potassium—Spectramox in Denmark, Augmentin in the United States) are effective in the treatment of childhood secretory otitis media. Among children who had at least 3 months of unresolving secretory otitis media, a 1-month administration of Augmentin is argued to be more effective than placebo treatment. To support those claims, in Fig 1 and in Tables 2, 3, and 4, the authors provide various exposures and analyses of the longitudinal data obtained in this 12-month-duration clinical trial that was completed in 1986.

The primary hypothesis, although not explicitly stated, seems to be that a 1-month antibiotic treatment for pediatric secretory otitis media as measured over a 12-month observation period is efficacious. The critical examination of their results suggest that this article is scientifically flawed and the efficacy conclusion of antibiotics cannot be supported with the data presented in the article.

Without having access to the primary data of this clinical trial and without knowing what statistical tests were conducted (in the "Methods" section the authors do not provide any information on statistics), the following comments will demonstrate some of the errors and scientific lapses in the article:

1. The primary end point—time with normal tympanogram, measuring disease-free periods—is shown in Table 2 of the article. The authors, with the information depicted in Table 2, assert that there exist "highly significant" differences ($P < .0001$) between the two treatment groups. Close scrutiny of Table 2 reveals that, during the 12-month period of the study, the average number of total follow-up days for the antibiotic group and for the placebo group were substantially different (299 days vs 372 days). Obviously, this is either a serious error or an impossible claim. The re-examination of the significant cure-rate difference between the two groups, with the additional information from Table 3 of the article, shows that the average time with normal tympanogram in the antibiotic-treated group is not significantly different from what is observed for the placebo group (0.494 vs 0.386, $P > .53$).

Those incorrect conclusions concerning the primary end point reached by the authors is due to the miscalculated disparate periods of observation among the two treatment groups and is also due to the creation of an artificial continuous variable (days) from discrete observations in time (status at monthly visits). The use of days as the measure of end-point analysis hyperinflates the true differences among groups. The significant statistical differences as reported would be in error if the nonindependence of the successive observations on individual subjects were not accounted for. This would apply equally to discrete and pseudocontinuous variables.

2. Recognizing the importance of laterality on the outcome, the authors show that the antibiotic effect remains significant for both unilateral and bilateral cases of otitis media (Table 3 of the article). However, those significant differences may be an artifact, ie, creation of a continuous variable—days with normal tympanograms without correcting for repeated measures. Those significant differences may not exist among the two treatment groups if the discrete primary data (monthly visits) are not converted into a pseudocontinuous variable (days). This is illustrated in Table 1, where the results are expressed as a proportion of time without disease (assuming 365 days in the 12-month observation period of the clinical trial). As shown in Table 1, the authors' antibiotic efficacy claim is not substantiated.

3. In Table 4 of the article, the authors show that the significant efficacy of antibiotic treatment is present for all age groups. They state that "there is a highly significant difference ($P < .0001$), with better tympanograms, in all three age groups." Once again, what the authors are claiming may be an artifact of data handling as explained above. Table 2 shows that no obvious and significant antibiotic effect is present for any of the three age groups in the study population when conservative assumptions are employed.

4. In Fig 1 of the article, the authors summarize the 12-month longitudinal data using a cross-sectional analysis, ie, the monthly disease incidence. They assert that "it is demonstrated in Fig 1 that the improvement persisted up to 8 months." This is incorrect. The close examination of this graph in Table 3 shows that the authors claim of the 8-month (persistent) improvement cannot be sustained under statistical considerations. Of the 12 observation points, only 2 (the first and the fifth month) show significant differences ($P < .01$). This incidence graph is also misleading because it does not provide longitudinal information such as one may gather from a life-table analysis. The graph in Fig 1 is not helpful to answer the patient response profile. It can only be taken as an illustration of group differences at monthly visits. There seems to be only a short-term efficacy (not a persistent benefit) at the 1-month visit, immediately after the termination of treatment. The only other significant difference between the two groups (the 5-month visit delayed effect) is difficult to explain by known biological reasons and rationale. Moreover, the authors in Table 7 of the article clearly demonstrate that there are no delayed beneficial effects due to the antibiotic treatment.

This apparent and anomalous difference is probably due to the strong effect of *confounders* (not included in the analysis by the authors). Confounding factors like the episodes of acute otitis media, the new onset of secretory otitis media, upper respiratory infections, treatments with antibiotics, and viral and seasonal effects may play stronger influences on the outcome than the Augmentin effect. A complex analysis, as described in item 7, may be necessary to understand the meaning of this "delayed" effect or artifact at the 5-month visit.

5. In order to describe the differences in response profiles between the two treatment groups, some form of life-table analysis (Mantel-Cox statistics, Breslow statistics) or event time distributions (Kaplan-Meier statistics) is essential. For good science, the following life-tables may be needed: (1) first normal tympanogram, (2) first abnormal tympanogram after normal (recurrence), (3) first acute otitis media, (4) first normal tympanogram after acute otitis media, (5) second acute otitis media, and (6) two consecutive months with normal tympanograms.

6. The antibiotic-treated group has recurrence problems that require explanation and further data analysis. The first-month difference of 0.30 between the two treatment groups is diminished at the second month (0.10, see Table 3). That disappearance of

Table 1.—Laterality and Proportion of Time With Normal Tympanograms

	Antibiotic	Placebo	Difference	z	P*
Unilateral	0.561 (n = 29)	0.398 (n = 24)	0.163	1.18	>.12
Bilateral	0.470 (n = 82)	0.382 (n = 86)	0.088	1.15	>.12
Total	0.494 (n = 111)	0.386 (n = 110)	0.108	1.62	>.05

*Significance levels are based on the conservative assumption of perfectly correlated observations within subjects.

Table 2.—Age and Proportion of Time With Normal Tympanograms

Age Group, y	Antibiotic	Placebo	Difference	z	P*
1-3	0.489 (n = 33)	0.417 (n = 27)	0.072	0.56	>.29
3-5	0.511 (n = 33)	0.349 (n = 34)	0.162	0.09	>.09
5-10	0.486 (n = 45)	0.393 (n = 49)	0.093	0.18	>.18

*Significance levels are based on the conservative assumption of perfectly correlated observations within subjects.

Table 3.—Proportion of Subjects With Normal Tympanograms at Monthly Visits

Months After Entry	Antibiotic	Placebo	Difference	χ^2	P
1	0.61*	0.31	0.30	20.48†	<.001
2	0.43	0.33	0.10	2.59	>.10
3	0.52	0.37	0.15	5.01	.026
4	0.47	0.41	0.06	0.79	>.10
5	0.56	0.33	0.23	11.98	<.001
6	0.44	0.33	0.11	3.04	>.05

*Computed from Fig 1; however, the proportions may not be completely accurate due to the reconstruction from a graphic display.

†Constant sample size (n = 111 and n = 110) is assumed for each visit since the authors do not indicate changes in sample size from visit to visit.

two thirds of the cure-rate difference between the groups within 1 month suggests a significant recurrence problem. Unfortunately, the scope of this recurrence problem is difficult to ascertain because the article has no information about patient response patterns. This short-term benefit and the recurrence issue have to be answered with an appropriate method of analysis.

7. The *primary end point* seems to be the measure of efficacy over a 12-month observation period. However, efficacy as measured after the termination of treatment appears to be an important *secondary end point.* With respect to this second end point, the data show significant differences among the treatment groups at the first-month visit (0.61 vs 0.31, $P < .001$). Although not sustained, this is an important efficacy claim that requires further probing.

A logistic regression type of analysis to account for the obvious effects of prognostic factors will determine whether this observed difference between the two groups is largely attributable to the Augmentin effect. The regression model should include, among other factors, entry status as well as pre-entry trends (prior 3 months of data). Factors such as natural history of disease in the cohort, laterality at pre-entry visits (including all three), hearing loss, and middle ear impedance magnitude and change (trend) must be considered in modeling the problem.

For the 12-month primary end-point analysis, more complex statistical models may be necessary to include the effects of confounders (item 4) in addition to the prognostic factors.

8. In this cohort, as shown in Fig 1, the natural history of secretory otitis media has two distinct patterns—large spontaneous cure rate (30%) within the first month followed by a flat-out incidence during the remaining 11 months. Both treatment groups seem to behave similarly after the second month, with very little extra remissions (see Table 7 of the article). This natural history pattern in the cohort raises several questions. Answers to those may be important to support or refute the present conclusions of efficacy. Those questions are: (1) What was the natural history prior to entry in the study? (2) Was it the same for both groups? (3) How many subjects were originally enrolled to be candidates? (4) What kind of patients fulfilled the consecutive 3-month disease requirement? (5) What patient's characteristics can describe those who were enrolled, but later excluded, because they had spontaneous cures by the third month? (6) What role did laterality play in this pre-entry natural history?

These questions are somewhat related to "If the present study is conducted with a different natural history, would the efficacy claim hold up?" For example, if the very same cohort is enrolled with the pre-entry requirement of 4 months of disease, the placebo group as shown in Table 3 would have only a 3% cure rate after 1 month into the study (not the 31% as is the present case). The response of the Augmentin group, under those conditions, would be entirely different. What would be the antibiotic efficacy under those circumstances?

9. The authors chose ear-based analysis rather than patient-based analysis. In other words, the experimental unit of this clinical trial is the "index ear" and not the "child." Therefore, the results would be interpreted accordingly and conservatively. Usually, ear-based analyses inflate the "true" cure rates. It is obvious that the observed cure in one ear of a bilaterally diseased child is *not* the same as curing the child (which requires cure of two ears). The extrapolation of index ear type of results to clinical efficacy may not be possible, or at least it will need more information about the status of the "other" ear.

The data analysis that includes dependence or independence of the "index" ear status to the "other" ear in subjects with both intact tympanic membranes at various visits is necessary before the authors' conclusions of efficacy can be justified.

10. The authors in this article do not reference their three previous publications of the same clinical trial.[2-4] One of those publications was based on an interim data analysis. This leads to several questions:

(1) Did the interim data analysis effect the termination of the study? (2)

Is the study population as enrolled and completed the same as the target sample size as designed? (3) What hypotheses and what assumptions were made to determine the sample size? (4) How were the interim analysis results accounted for in the final data analyses? (5) Why did the authors fail to reference their previous publications on the same data set? (6) Was the study supported by a grant or funding from a public or private source?

In conclusion, the scientific lapses and the unanswered questions related to data analysis discussed above cast substantial doubts on the findings of this study. Once again, the significant and long-term efficacy of antibiotic treatment for secretory otitis media remains to be proven.

For the advancement of science, I also suggest that the ARCHIVES should adopt the recent editorial policy of the *Journal of the American Medical Association*, and request that all authors deposit their primary data for the record. Such practice would augment the freedom of information exchange and would provide a valuable resource for other interested researchers in a given specialty.

ERDEM I. CANTEKIN, PHD
Pittsburgh, Pa

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2. Thomsen J, Sederberg-Olsen J, Stangerup SE, Balle V, Vejlsgaard R. Long-term antibiotic treatment of children with secretory otitis media: a double-blind placebo-controlled study. *Acta Otolaryngol (Stockh).* 1988;449:49-50.

3. Thomsen J, Sederberg-Olsen J, Stangerup SE, Balle V, Vejlsgaard R. Long-term antibiotic treatment of children with secretory otitis media: double-blind placebo-controlled study. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media: Proceedings of the Fourth International Symposium.* Toronto, Canada: BC Decker; 1988:244-247.

4. Thomsen J, Sederberg-Olsen J, Stangerup SE, et al. Long-term antibiotic treatment of children with secretory otitis media. In: Sade J. *Acute and Secretory Otitis Media. Proceedings of the International Symposium on Acute and Secretory Otitis Media.* Amsterdam, the Netherlands: Kugler Publications; 1986:432-437.

In Reply.—Thank you very much for giving us the opportunity to respond to the letter to the editor from Dr Cantekin concerning our study on antibiotic treatment of patients with secretory otitis media. In the middle of June, Dr Cantekin requested access to our raw data to reexamine our findings. He considered this to be an unusual request, and so did we. He also stated that any findings would be confidential and shared with us, and that we would have the final decision what to do with the findings.

We responded that we would not release the many thousands of data, but would be interested in reevaluating the data according to some specific questions of his choice if he would be interested. In the middle of October 1989 we received a letter, dated September 29, 1989, with a magnitude of questions, and expressing delight about our willingness to respond.

With this background, it is with some surprise that we receive the information that the same questions have been addressed to us via a letter to the editor in the ARCHIVES.

Before answering the special points we want to repeat and clarify that the primary hypothesis was to investigate if there was a difference in effect between antibiotic and placebo treatment for 1 month over a 12-month observation period. In order to detect a 20% difference with the significance $\alpha = 0.05$ and $\beta = 0.10$ (90% power), 127 patients per group would be needed, and were included.

1. In Table 2 there is, unfortunately, a misprint. Time with abnormal tympanogram for amoxicillin-clavulanate should read 182.4 days instead of 118.4. The total observation period is 363.1 days and 372.1 days, respectively, thus almost identical. The P value .002 is based on the correct time period. The comment by Dr Cantekin is subsequently inadequate. Furthermore, from Tables 3 and 4 it could be seen without difficulty that the figure 118.4 must be erroneous. Dr Cantekin also criticizes our use of the exact visit dates instead of grouping them together by month. We feel that using the exact visit dates more correctly reflects reality than creating a rather artificial month grouping. The observed differences are so large that it is inconceivable that such a grouping would yield a substantially different result.

2. Our comments above also apply to Dr Cantekin's second point. The P values in our Table 3 have regrettably been mixed up and should read .03, .06, and .004 for unilateral, and .02, .09, and .001 for bilateral. Time with abnormal tympanogram and time to first normal tympanogram are different with statistical significance in the two treatment groups.

3. Our comments for the first point apply. As the comparative groups are smaller, the differences between the treatment groups are statistically significant in about half the number of our calculations ($P < .05$) and nonsignificant in the other half ($P > .05$).

We are very much in doubt as to how Dr Cantekin has produced the P values in Tables 1 and 2, without having access to the raw data. With the data supplied in the article it is impossible to produce such an analysis, and it is incomprehensible how he can state that $P > .10$ unless he has used a totally inappropriate χ^2 test. This test is inappropriate because we are not dealing with dichotomous outcomes, but with percentages.

4. Concerning Dr Cantekin's Table 3, the P values produced yield the same type of pattern as in the original Fig 1, although he manhandles data. In fact we used the whole scale A, C1, C2, and B (using Wilcoxon 2 sample tests), as this is a more sensitive method. It is in fact an inappropriate (although common) method to analyze longitudinal data by applying statistical tests at successive time points, since a consistent pattern over the time points (as in this case) may well not reach significance at the individual time points. A more correct method would be to compare the time to certain events by life-table or survival analysis. We used a very similar approach by using Wilcoxon 2 sample tests for the variable "time to first normal tympanogram" as well as for "time with abnormal tympanogram" and the "time with normal tympanogram." In retrospect, the "best" variable (percentage observation time with abnormal tympanogram) was presented as a mean for the subgroups but the P values were not supplied (they are $P = .0056$ overall, $P = .041$ for unilateral, and $P = .054$ for bilateral infections).

Furthermore, Dr Cantekin has assumed that the sample size is constant over the period. This is not correct. Our figures are based on the actual size at each time. The number of patients decreases in the same way in the two groups over the whole period, and the average monthly decrease is 2.5%.

Confounders may indeed influence the outcome of a trial. In our trial the most annoying confounders were the bouts of acute otitis media and other infections during the 12-month control period requiring antibiotic treatment. We have taken this into account, and excluded the first tympanogram after such an episode; this had no effect on the incidence of secretory otitis media as depicted in Fig 1. The confounding effect of an antibiotic course is mentioned in the article.

5. The life-table analysis proposed by Dr Cantekin is exactly how we have handled the data concerning points 1 and 2. Life-table analysis for points 3, 4, and 5 could have been produced since the information is available. However, this was considered irrelevant for the scope of our study, and therefore it was not mentioned.

6. We do not believe that the antibiotic-treated group had recurrence problems more than the placebo group had. In Table 7 it is clearly seen that the outcome of tympanometry in the 12 months following termination of treatment is only dependent on the tympanometric condition at treatment termination, with no difference between antibiotic and placebo treatment. This question by Dr Cantekin is therefore superfluous.

7. It has not been the aim of our study to clarify the importance of a large number of prognostic factors. Most important for the comparisons between the groups is that they are not different in any respect. This is also what has been stated in the publication. Again we find the question misleading and irrelevant.

8. As mentioned in the "Patients and Methods" section in our article, a detailed social, family, and patient history was obtained in all patients. The two groups were quite comparable with regard to age, sex, family disposition, social background, previous ear-nose-throat-related diseases, and season of entry. The mean age was 4.4 years in both the active and the placebo treatment groups. The natural history is therefore the same in the two groups (points 1 and 2); 773 subjects were originally enrolled to be candidates and of the 269 subjects who fulfilled the inclusion criteria, 5 refused to participate, enrolling a total of 264 children in the trial. Those with spontaneous cures by the third month had the same characteristics as those included in the study, including distribution of laterality (points 3, 4, 5, and 6).

9. The comment in Dr Cantekin's point 9 is irrelevant. One ear per patient has been studied regardless of laterality of the disease. "In patients with bilateral disease, insertion of a ventilating tube in the right ear was performed, whereas the left ear was included in the study."

10. One interim analysis was carried out and has been presented at three meetings. The analysis did not effect the termination of the study (point 1). The study population as enrolled and completed is the same as the target sample as designed, and the sample size has already been described above (points 2 and 3). The interim analysis has not affected the final analysis, and is therefore not accounted for in the final analysis (point 4), and it is purely for practical reasons (reducing the number of references) that the interim reports have not been cited.

In conclusion, we want to maintain our statement that 1 month of treatment with amoxicillin-clavulanate significantly shifts the individual patient from a poor tympanometric condition (types C2 and B) to a better condition (types A and C1), compared with placebo treatment. Because a type A middle ear condition has a more favorable course over a given period than a type B middle ear condition, the antibiotic treatment induces a prolonged improvement of the middle ear status.

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A Significant New Contribution to Radical Head and Neck Surgery

To the Editor.—Ward and coworkers[1] introduce a new technology in the article "A Significant New Contribution to Radical Head and Neck Surgery: the Argon Beam Coagulator as an Effective Means of Limiting Blood Loss." I had the pleasure of hearing Dr Ward's presentation at the American Society of Head and Neck Surgery and to see the videotape of the instrument "in action." Although I share his enthusiasm for the potential capabilities of this new instrument, I would like to raise a specific safety issue.

The argon beam coagulator depends on the flow of a stream of argon gas to blow away blood and other fluids in front of the coagulating current. The argon gas stream is described as "gentle," but no quantitative information is given with regard to its force. My question relates to the extent with which blood "blown away" from the operative field is aerosolized.

Although there is no similar technology with which to compare, we know from laser aerosolization studies[2,3] that live bacteria and viruses can be recovered from laser plumes. Whether viable cancer cells can be recovered is not certain.[4] It has long been appreciated that tubercular organisms can be aerosolized during cadaver dissection. Early in this century many medical students acquired tuberculosis during gross anatomy class. The recognition that aerosols can carry viable infectious agents has led to the standard laboratory practice of using laminar flow hoods for handling potentially contaminated fluids.[5]

If the aerosol created by the blood "blown away" from the wound does contain viable infectious agents, at what risk are surgical personnel? Surgical masks are not designed to filter inhaled air for viruses, and not all patients and staff may be wearing masks. The Centers for Disease Control, Atlanta, Ga, has recommended that eye protection be worn where there is potential for splashing body fluids.[6] However, is conventional eye protection adequate for aerosolized infectious particles?

The author's statement that the argon beam coagulator "reduces the operating teams' exposure to the patient's blood, tissue, and transfusion products" may not take into consideration aerosolized blood and other body fluids. Although it is unlikely that the human immunodeficiency virus would be transmitted in viable form by aerosol,[7] there are other agents with the potential. Before advocating the widespread use of this new technology, an evaluation of argon beam coagulator aerosol content, particulate concentration, and duration should be made. The risk to health care providers should be carefully assessed and, if necessary, appropriate safety precautions developed.

MAJ CARL A. PATOW, MC, USA
Washington, DC

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3. Mullarky MB, Norris CW, Goldberg ID. The efficacy of the CO_2 laser in the sterilization of skin seeded with bacteria: survival at the skin surface and in the plume emissions. *Laryngoscope.* 1985;95:186-187.

4. Oosterhuis JW, Verschueren RCJ, Eibergen R, Oldhoff J. The viability of cells in the waste products of CO_2 laser evaporation of cloudman mouse melanomas. *Cancer.* 1982;49:61-67.

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6. Centers for Disease Control. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. *MMWR.* 1988; 37:377-382, 387-388.

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News and Comments

International Society for the History of Otolaryngology: Call for Papers.—If you have an interest in the history of medicine, especially the history of otolaryngology, and have material that you believe would make an interesting presentation for the annual meeting of the Society at the time of the Annual Meeting of the American Academy of Otolaryngology-Head and Neck Surgery, to be held in October 1990 in San Diego, Calif, please submit an abstract with your potential presentation. Abstracts should be sent to Loring W. Pratt, MD, 37 Lawrence Ave, Fairfield, ME 04937.

Maurice H. Cottle Honor Award.—The American Rhinologic Society wishes to announce the competition for the Maurice H. Cottle Honor Award. The manuscript submitted should represent basic rhinologic research. The winner of the competition for this award will receive a check for $1000 and will be requested to present the winning manuscript at the annual scientific meeting, which will be held on Saturday, September 8, 1990, in San Diego, Calif. Please submit your manuscripts to Dr George Facer, Secretary, American Rhinologic Society, 200 First St SW, Rochester, MN 55905, by June 1, 1990.

1991 Research Grants Available.—The Deafness Research Foundation invites applications for its 1991 grants in support of new research that promises to advance our understanding of the causes, treatment, and prevention of deafness and related ear disorders. The grants will be awarded to tax-exempt institutions for projects that will begin January 1, 1991, with the principal investigator of each project a member of the staff or faculty of such institution. The grants do not exceed $15 000, and can be competitively renewed with the same limit for an additional 1 or 2 years. Applications are reviewed for the scientific merit of the proposed investigations and for their direct or potential clinical importance. The deadline for first-year applications is July 15, 1990; for renewal applications, August 15, 1990. For full information on the grants program, and for the required application form, contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 E 38th St, New York, NY 10016.

Otological Research Fellowship for Third-Year Medical Students.—The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a 1-year block of time at the end of the third year of medical school—thus requiring a 1-year leave of absence from the medical school curriculum. Applications for 1991 funding must be received by November 15, 1990. For more information about this fellowship, contact: Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 E 38th St., New York, NY 10016; (212) 684-6556.

Election of Officers Announced.—The Otolaryngology-Head and Neck Surgery Section of the Puerto Rico Medical Association announces that Pablo M. López Baez, MD, and Lionel Fernández López, MD, have been elected president and secretary, respectively.

Endoscopic Sinus Surgery: A Continuing Medical Education Course.—The Office of Continuing Medical Education of the University of Michigan Medical School is sponsoring an upcoming course entitled "Endoscopic Sinus Surgery." This course, which will be held on August 17 and 18, 1990, at the Towsley Center, Ann Arbor, Mich, is presented by faculty of the departments of otolaryngology of the University of Michigan (Charles F. Koopman, Jr, MD) and Johns Hopkins University, Baltimore, Md (David W. Kennedy, MD) This course is designed to give the participant both theoretical and practical knowledge concerning endoscopic sinus surgery. On both days, course participants will attend didactic lectures followed by hands-on anatomic dissection on cadavers. Fifteen hours of Category 1 credit will be offered. For further information, contact Teresa Mitchell, Program Assistant, Office of Continuing Medical Education, G-1100 Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.

Symposium on the Medical Problems of Musicians and Dancers.—From August 2 through 5, 1990, The Cleveland (Ohio) Clinic Foundation, in joint sponsorship with the Aspen (Colo) Music Festival and the Performing Arts Medicine Association, will present a continuing medical education program entitled "The Eighth Annual Symposium on Medical Problems of Musicians and Dancers." This course has been approved for Category 1 credit and will be held at the Wheeler Opera House, Aspen. For further information, contact The Cleveland Clinic Foundation, Department of Continuing Education, 9500 Euclid Ave, Room TT-31, Cleveland, OH 44195-5241; 444-5696 (local); (800) 762-8173 (other).

Postgraduate Course in Current Concepts in Radiology.—Harvard Medical School, Boston, Mass, is sponsoring a postgraduate course on current concepts in head and neck radiology, neuroradiology, and neurologic magnetic resonance imaging. This course will be held from October 1 through 5, 1990, at The Lafayette Hotel, Boston. Forty hours of Category 1 credit will be offered. For further information, contact the Department of Continuing Medical Education, Harvard Medical School, Boston, MA 02114; (617) 432-1525.

Federation Announces National Congress.—The Federation of Otolaryngology of Mexico announces that its Twelfth Annual Congress will be held from October 1 through 5, 1990, at Monterrey, Mexico. For further information, contact Sergio Decannini, MD, Aldama 415 Sur, Monterrey, Nuevo León 64000, Mexico; telephone, 43 1246.

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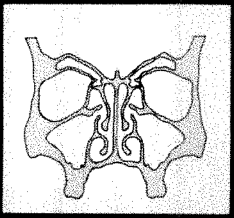

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WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2-1006 March 1989

REFERENCES: **1.** Kaliner MA. Pathogenesis of the late phase reaction and the mechanisms of action of corticosteroids in the treatment of allergic diseases. *N Engl Reg Allergy Proc.* 1986;7(3):1-5. **2.** Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol.* 1989;83(3):627-633. **3.** Salomonsson P, Gottberg L, Heilborn H, Norrlind K, Pegelow K-O. Efficacy of an oral antihistamine, astemizole, as compared to a nasal steroid spray in hay fever. *Allergy.* 1988;43(3):214-218. **4.** Beswick KBJ, Kenyon GS, Cherry JR. A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis. *Curr Med Res Opin.* 1985;9(8):560-567. **5.** Knight A, Kolin A. Long term efficacy and safety of beclomethasone dipropionate aerosol in perennial rhinitis. *Ann Allergy.* 1983;50(2):81-84.

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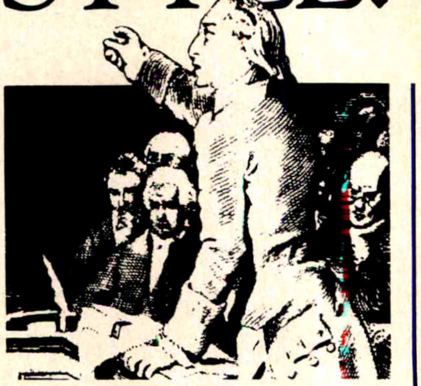

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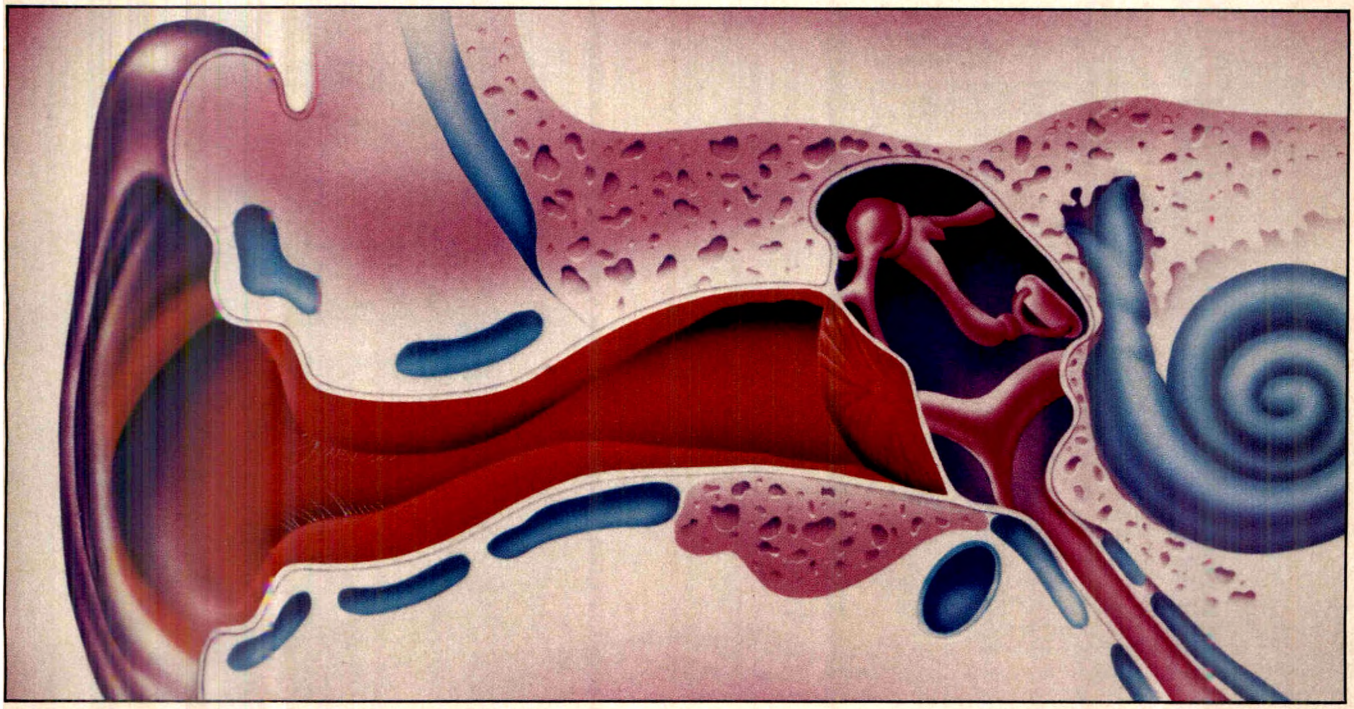

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VōSoL® HC
OTIC SOLUTION
(hydrocortisone and acetic acid otic solution, USP)

VōSoL®
OTIC SOLUTION
(acetic acid otic solution, USP)

Please see full prescribing information on next page.

*No resistant strains of susceptible organisms have been reported in vitro. (Does not necessarily imply a correlation with clinical results.)

References: 1. Ordonez GE, Kime CE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: I. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-polymyxin B otic solutions. *Curr Ther Res.* 1978;23(May suppl):SS3-SS14.
2. Kime CE, Ordonez GE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: II. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-colistin otic solutions. *Curr Ther Res.* 1978;23(May suppl):SS15-SS28.
3. Glassman JM, Pillar J, Soyka JP. Otitis externa: comparative *in vitro* sensitivities of clinical isolates of bacteria and fungi to nonantibiotic and antibiotic otic preparations. *Curr Ther Res.* 1978;23(May suppl):SS29-SS38.

Specify: Brand Medically Necessary, Dispense as Written

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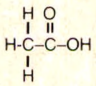
VōSoL® HC
OTIC SOLUTION
(hydrocortisone and
acetic acid otic solution, USP)

VōSoL®
OTIC SOLUTION
(acetic acid otic solution, USP)

Description: VōSoL (acetic acid otic solution, USP) is a solution of acetic acid (2%), in a propylene glycol vehicle containing propylene glycol diacetate (3%), benzethonium chloride (0.02%), and sodium acetate (0.015%).
VōSoL HC (hydrocortisone and acetic acid otic solution, USP) also contains hydrocortisone (1%) and citric acid (0.05%). The empirical formulas for acetic acid and hydrocortisone are CH_3COOH and $C_{21}H_{30}O_5$, with a molecular weight of 60.05 and 362.46, respectively. The structural formulas are:



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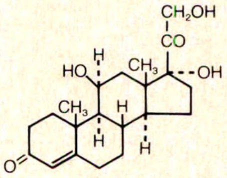

Acetic Acid

Chemically, hydrocortisone is:
Pregn-4-ene-3,20-dione,
11,17,21-trihydroxy-,(11β)-.

VōSoL and VōSoL HC are available as nonaqueous otic solutions buffered at pH 3 for use in the external ear canal.
Clinical Pharmacology: Acetic acid is anti-bacterial and anti-fungal; propylene glycol is hydrophilic and provides a low surface tension; benzethonium chloride is a surface active agent that promotes contact of the solution with tissues; hydrocortisone (in VōSoL HC) is anti-inflammatory, anti-allergic and anti-pruritic.
Indications and Usage: VōSoL — For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial.
VōSoL HC — For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation.
Contraindications: Hypersensitivity to any of the ingredients. VōSoL HC is contraindicated in vaccinia and varicella. Perforated tympanic membrane is considered a contraindication to the use of any medication in the external ear canal.
Warnings: Discontinue promptly if sensitization or irritation occurs.
Precautions: Transient stinging or burning may be noted occasionally when the solution is first instilled into the acutely inflamed ear.
Adverse Reactions: Stinging or burning may be noted occasionally; local irritation has occurred very rarely.
Dosage and Administration: Carefully remove all cerumen and debris to allow VōSoL to contact infected surfaces directly. To promote continuous contact, insert a wick saturated with VōSoL or VōSoL HC into the ear canal; the wick may also be saturated after insertion. Instruct the patient to keep the wick in for at least 24 hours and to keep it moist by adding 3 to 5 drops of VōSoL or VōSoL HC every 4 to 6 hours. The wick may be removed after 24 hours but the patient should continue to instill 5 drops of VōSoL 3 or 4 times daily thereafter, for as long as indicated.
How Supplied: VōSoL Otic Solution, in 15 mL (NDC 0037-3611-10) and 30 mL (NDC 0037-3611-30) measured-drop, safety-tip plastic bottles.
VōSoL HC Otic Solution, in 10 mL measured-drop, safety-tip plastic bottle (NDC 0037-3811-12).
Storage: Store at room temperature; avoid excessive heat. Keep container tightly closed.
Rev. 5/89

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- better compliance because transdermal delivery is more convenient

Transderm Scōp®
scopolamine
programmed delivery
0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

CIBA

Transderm Scōp®

scopolamine

(formerly Transderm-V)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

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C88-5 (Rev. 2/88)

CIBA

References:

1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine (*P* = 0.01) and placebo (*P* = 0.003).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® (*P*>0.05).

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RYNATAN® B.I.D.
ITRATABLE TABLETS

ch capsule-shaped tablet contains: phenylephrine tannate, 25 mg; orpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

RYNATAN®-S* B.I.D.
PEDIATRIC SUSPENSION

Each teaspoonful (5 mL) contains: phenylephrine tannate, 5 mg; chlorpheniramine tannate, 2 mg; pyrilamine tannate, 12.5 mg.

ent pending. RYNATAN®-S is the combination of RYNATAN® Pediatric Suspension oz) and a 10 mL calibrated oral syringe.

en used for symptomatic relief of coryza and nasal congestion in allergic rhinitis or common cold.

ase see the following page for prescribing information.

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RYNATAN® B.I.D.
TITRATABLE TABLETS

Each capsule-shaped tablet contains: phenylephrine tannate, 25 mg; chlorpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

RYNATAN®-S* B.I.D.
PEDIATRIC SUSPENSION

Each teaspoonful (5 mL) contains: phenylephrine tannate, 5 mg; chlorpheniramine tannate, 2 mg; pyrilamine tannate, 12.5 mg.

Description RYNATAN® is an antihistaminic/decongestant combination available for oral administration as *Tablets* and as *Pediatric Suspension.* Each tablet contains:

Phenylephrine Tannate	25 mg
Chlorpheniramine Tannate	8 mg
Pyrilamine Tannate	25 mg

Other ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, methylcellulose, polygalacturonic acid, talc.

Each 5 mL (teaspoonful) of the Pediatric Suspension contains:

Phenylephrine Tannate	5 mg
Chlorpheniramine Tannate	2 mg
Pyrilamine Tannate	12.5 mg

Other ingredients: benzoic acid, FD&C Red No. 3, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, sucrose.

Clinical Pharmacology RYNATAN combines the sympathomimetic decongestant effect of phenylephrine with the antihistaminic actions of chlorpheniramine and pyrilamine.

Indications and Usage RYNATAN is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications RYNATAN is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery while using this product.

Drug interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, mutagenesis, impairment of fertility: No long term animal studies have been performed with RYNATAN®.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with RYNATAN. It is also not known whether RYNATAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RYNATAN should be given to a pregnant woman only if clearly needed.

Nursing mothers: RYNATAN should not be administered to a nursing woman.

Adverse Reactions Adverse effects associated with RYNATAN at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Overdosage *Signs and symptoms:* May vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment: Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration Administer the recommended dose every 12 hours.
RYNATAN Tablets: Adults — 1 or 2 tablets.
RYNATAN Pediatric Suspension: *Children over six years of age* — 5 to 10 mL (1 to 2 teaspoonfuls); *Children two to six years of age* — 2.5 to 5 mL (½ to 1 teaspoonful); *Children under two years of age* — Titrate dose individually

How Supplied RYNATAN® Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and 500 (NDC 0037-0713-96).

RYNATAN® Pediatric Suspension: pink with strawberry-currant flavor, in 4 fl. oz. bottles (NDC 0037-0715-67, labeled RYNATAN®-S*) and in pint bottles (NDC 0037-0715-68).

Storage: RYNATAN® Tablets — Store at room temperature; avoid excessive heat — above 40°C (104°F).

RYNATAN® Pediatric Suspension — Store at controlled room temperature — between 15°C–30°C (59°F–86°F); protect from freezing.

**Patent Pending*

RYNATAN®-S is the combination of RYNATAN Pediatric Suspension (4 fl. oz.) and a 10 mL, calibrated, oral syringe.

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Cranbury, New Jersey 08512

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Classified Advertising

All classified advertising orders, correspondence and payments should be directed to: Archives of Otolaryngology, P.O. Box 1510, Clearwater, Florida 34617. Our telephone numbers are: National 800-237-9851; in Florida 800-553-8288; Local 813-443-7666. Please do not send classified ads, payments or related correspondence to the AMA headquarters in Chicago. This causes needless delay.

Inquiries about "BOX NUMBER" advertisements: All replies must be in writing and must cite the box number in the ad. Example: Box ______, c/o AOTO, P.O. Box 1510, Clearwater, Florida 34617. We are not permitted to divulge the identity of advertisers who wish their mail sent in care of Archives of Otolaryngology.

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One-third page	333	306
One-sixth page	222	204
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OTOLARYNGOLOGIST — BC/BE to join main branch of thirty-five physician, multi-specialty group. Excellent clinic and hospital facilities. Very competitive salary and benefit package. Excellent opportunity. Good hunting, fishing. Good schools, a beautiful place to raise a family. Call Executive Administrator collect, (701) 857-0236. Or write: Medical Arts Clinic, P.C., P.O. Box 1489, Minot, ND 58702-1489.

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Please send curriculum vitae to:

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LaPorte, IN 46350

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OTOLARYNGOLOGY Consultants of Memphis — Expanding three-doctor group seeks pediatric, fellowship-trained associate to join a diverse, quality oriented and busy practice. Four fully staffed offices. Associated with the areas major medical centers. Competitive salary and comprehensive benefits. Opportunities leading to partnership after two years. Please direct inquiries and CV to: Thomas E. Long, MD; Rande H. Lazar, MD, 848 Adams, Suite 401, Memphis, TN 38103.

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Board-certified/board-eligible otolaryngologist needed for busy four-person practice in Milwaukee. Outstanding opportunity in well known group practicing all aspects of our specialty. Send CV to:

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Send CV to: Barbara Volk
Santa Barbara Medical Foundation Clinic
P.O. Box 1200, Santa Barbara, CA 93102.

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OTOLARYNGOLOGIST
Durham, North Carolina

Private Eye, Ear, Nose and Throat Hospital and Clinic in Piedmont, North Carolina looking for fourth otolaryngologist in busy private practice with academic affiliation. Prefer otology background. Please send curriculum vitae or call: Charles H. Mann, MD, Department of Otolaryngology, McPherson Hospital, 1110 West Main Street, Durham, NC 27701. (919) 682-9341.

WALNUT CREEK, CALIFORNIA — We are seeking a BC/BE general otolaryngologist to join three-person department. High-growth, white collar suburban Bay area. Fully referred, broad spectrum practice. Experienced or 1990 graduate considered. For more information, please send CV to: Glenn Schneider, MD, The Permanente Medical Group, Inc., 1425 South Main Street, Walnut Creek, CA 94596. EOE.

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PART-TIME PEDIATRIC otolaryngologist, Department of Otolaryngology-HNS, Indiana University, School of Medicine. Candidates should be board-certified and have completed a pediatric fellowship with interest and prior experience in research, teaching and patient care. Send curriculum vitae to: R.T. Miyamoto, MD, Professor and Chairman, 702 Barnhill Drive, Suite A-56, Indianapolis, IN 46202-5230. (IU is an EEOC employer.)

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PHYSICIAN having a strong academic interest in vestibular and/or ocular motor systems is sought at the assistant/associate professor level. A joint tenure appointment in the Department of Otology and Laryngology, and the Department of Neurology, Harvard Medical School is envisioned. Activities include: seeing patients complaining of imbalance, interpretation of vestibular diagnostic tests, and vestibular/ocular motor research projects. Candidate should demonstrate ability to generate grant funding. Please contact: Conrad Wall, III, PhD, Vestibular Lab; or Robert Levine, MD, Eaton Peabody Lab, Massachusetts Eye & Ear Infirmary, 243 Charles Street, Boston, MA 02114.

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The Division of Otolaryngology/Head and Neck Surgery, Stanford University Medical Center is seeking to fill an incremental full-time position at the assistant professor level. Applicants should be eligible to become board-certified or board-certified in otolaryngology with a subspecialty interest in otology. The successful applicant should have an interest in developing a strong clinical program in otology/neuro-otology and have demonstrated potential for research and teaching. Approximately 60% of the applicant's time will be devoted to clinical care and teaching, and 40% to research. Although not mandatory, a fellowship in otology/neuro-otology is desirable. Applications for the position will be accepted until November 1990. Starting date of the position to be negotiated.

Stanford University is committed to increasing representation of women and members of minority groups on its faculty and particularly encourages applications from such candidates.

Letters of inquiry and curriculum vitae should be sent to:

Willard E. Fee, Jr., MD
Division of Otolaryngology/Head and Neck Surgery
STANFORD UNIVERSITY MEDICAL CENTER
Stanford, CA 94305-5328
(415) 725-6500

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Harvard Medical School

seeks a

PEDIATRIC OTOLARYNGOLOGIST

at the

Instructor/Assistant Professor Level

Requirements include board-certification, fellowship training or other experience in pediatric otolaryngology, and abilities in clinical or basic research.

Contact: **Roland D. Eavey, MD**
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114

The Massachusetts Eye and Ear Infirmary is an equal opportunity/affirmative action employer. Female and minority candidates are encouraged to apply.

Academic Position in Otolaryngology

The Department of Otolaryngology of the Boston University School of Medicine seeks a full time, Board certified otolaryngologist with a primary interest in otology/neurotology for July 1, 1990. A strong interest in research and teaching is desirable. Please send inquiries and curriculum vitae to:

Nabil S. Fuleihan, MD
Department of Otolaryngology
Boston University School of Medicine
88 East Newton Street
Boston, MA 02118

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This position is tenure earning. Academic rank and salary will be commensurate with the candidate's experience and qualifications.

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Thomas J. Balkany, MD
Professor and Vice-Chairman
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Rande H. Lazar, MD
Director of Fellowship Training

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Department of Otolaryngology
Le Bonheur Children's Medical Center
Memphis, TN 38103

Otolaryngologist

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JULY 1, 1991

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The fellowships are under the direction of Charles D. Bluestone, MD and Sylvan E. Stool, MD.

Contact:

Department of Pediatric Otolaryngology
CHILDREN'S HOSPITAL OF PITTSBURGH
One Children's Place
3705 Fifth Avenue at DeSoto Street
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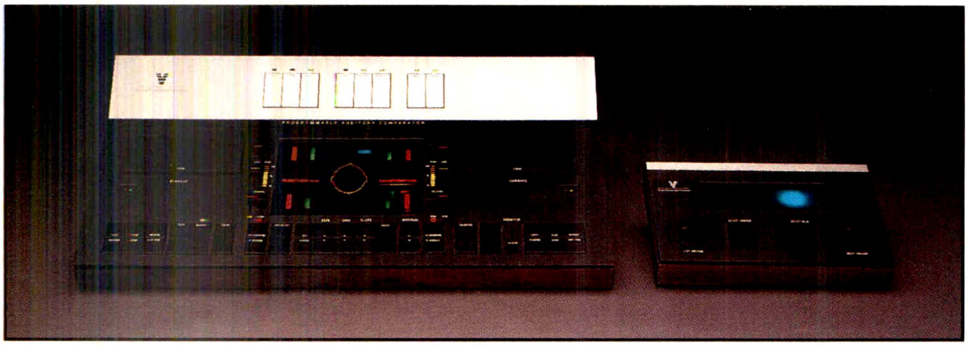

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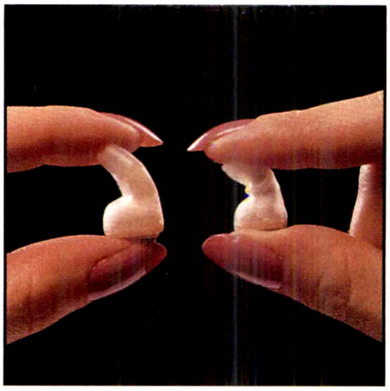
The Quantum® is also one of the best sounding hearing aids available on the market today. By delivering the sound closer to the eardrum, safely and effectively, patients require less electronic amplification to meet their needs. So, the Quantum® sounds more natural!



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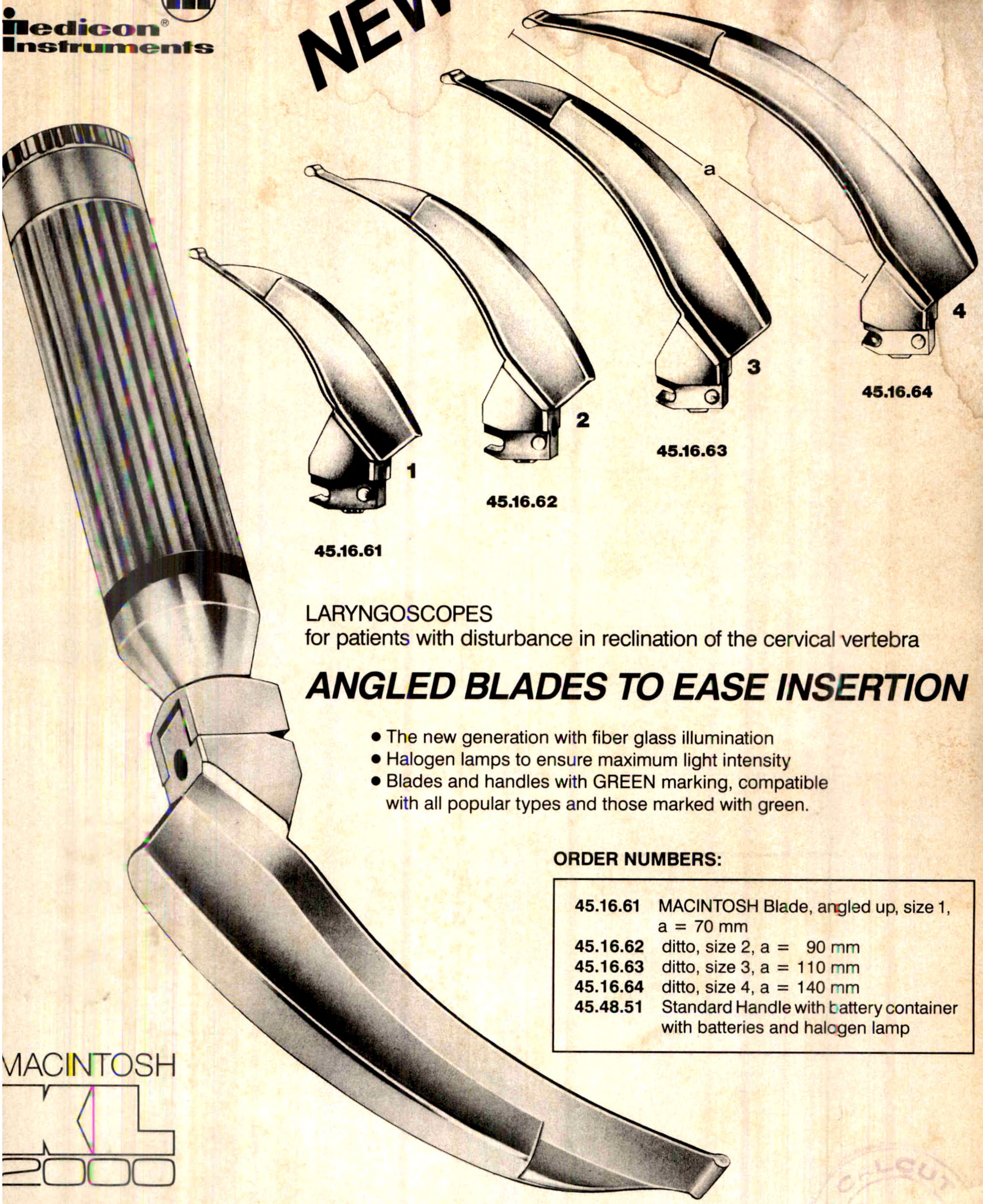

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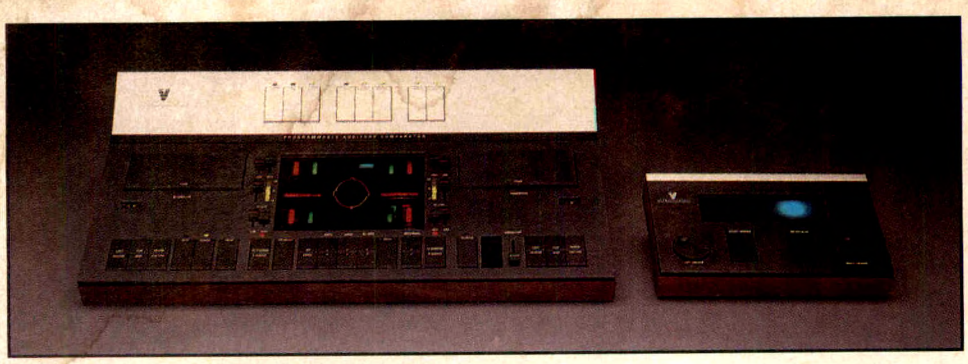

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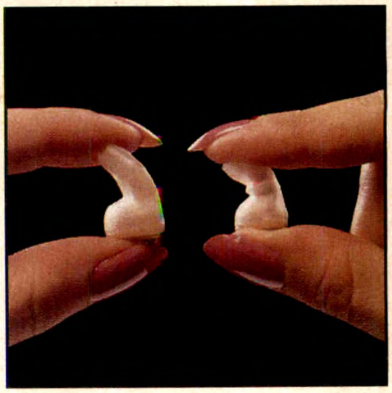

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VOLUME 116, NUMBER 6, JUNE 1990

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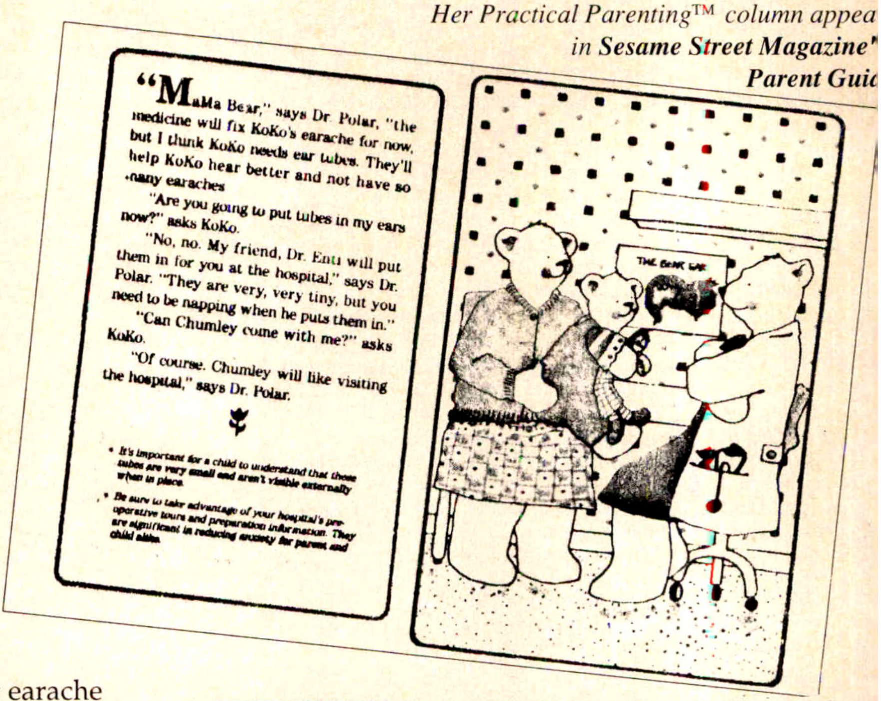

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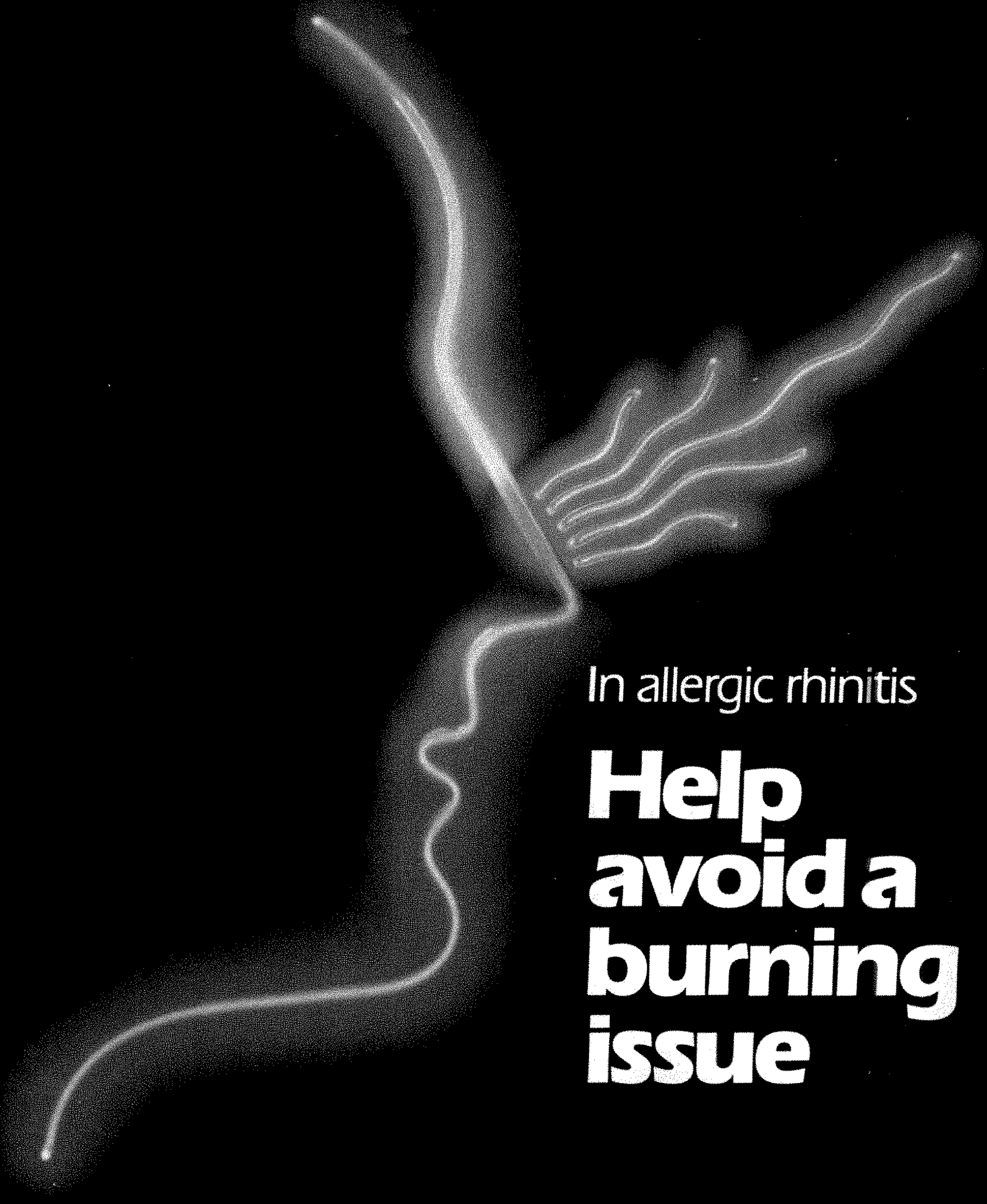
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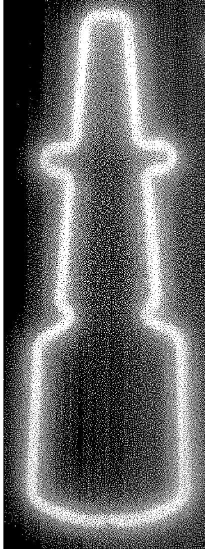

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Please see brief summary of prescribing information and references on following page.

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References: 1. Bronsky EA, Tarpay M, Tinkelman DA, Bush JK. A comparison of two dosing regimens of beclomethasone dipropionate aqueous nasal spray and flunisolide nasal spray in the treatment of acute seasonal rhinitis. *Immunol & Allerg Pract.* 1987;IX(5):165/11-170/16. **2.** Anderson P, Boyd G, Chatterjee SS, et al. A comparison of beclomethasone dipropionate aqueous nasal spray and beclomethasone dipropionate pressurized nasal spray in the management of seasonal rhinitis in adults and children. Clinical study report, 1985. **3.** Morrow-Brown H, Jackson FA, Pover GM. A comparison of beclomethasone dipropionate aqueous nasal spray and sodium cromoglycate nasal spray in the management of seasonal allergic rhinitis. *Allergol Immunopathol.* 1984;12:355-361.

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INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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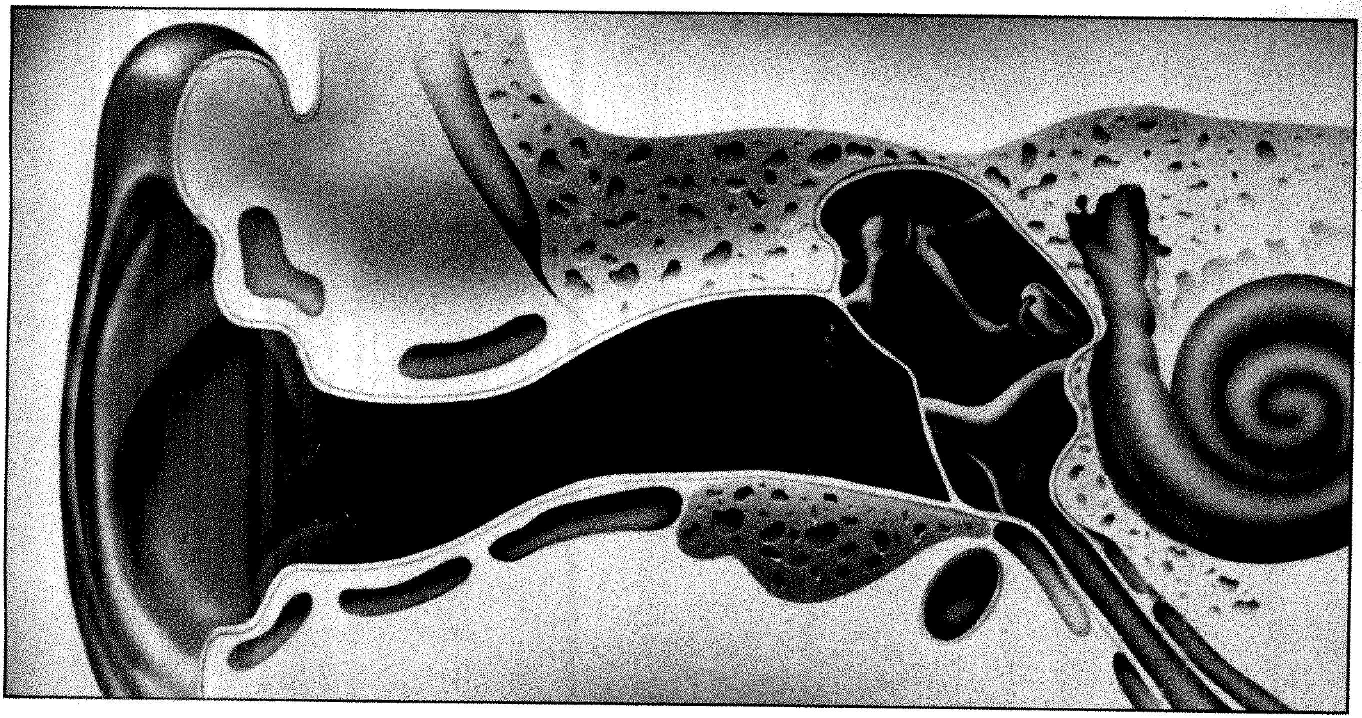

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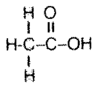

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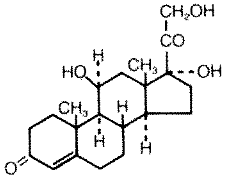

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Precautions: Transient stinging or burning may be noted occasionally when the solution is first instilled into the acutely inflamed ear.
Adverse Reactions: Stinging or burning may be noted occasionally; local irritation has occurred very rarely.
Dosage and Administration: Carefully remove all cerumen and debris to allow VōSoL to contact infected surfaces directly. To promote continuous contact, insert a wick saturated with VōSoL or VōSoL HC into the ear canal; the wick may also be saturated after insertion. Instruct the patient to keep the wick in for at least 24 hours and to keep it moist by adding 3 to 5 drops of VōSoL or VōSoL HC every 4 to 6 hours. The wick may be removed after 24 hours but the patient should continue to instill 5 drops of VōSoL 3 or 4 times daily thereafter, for as long as indicated.
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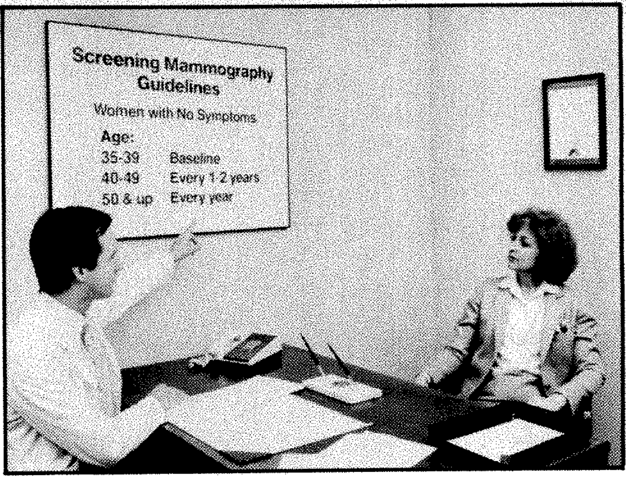

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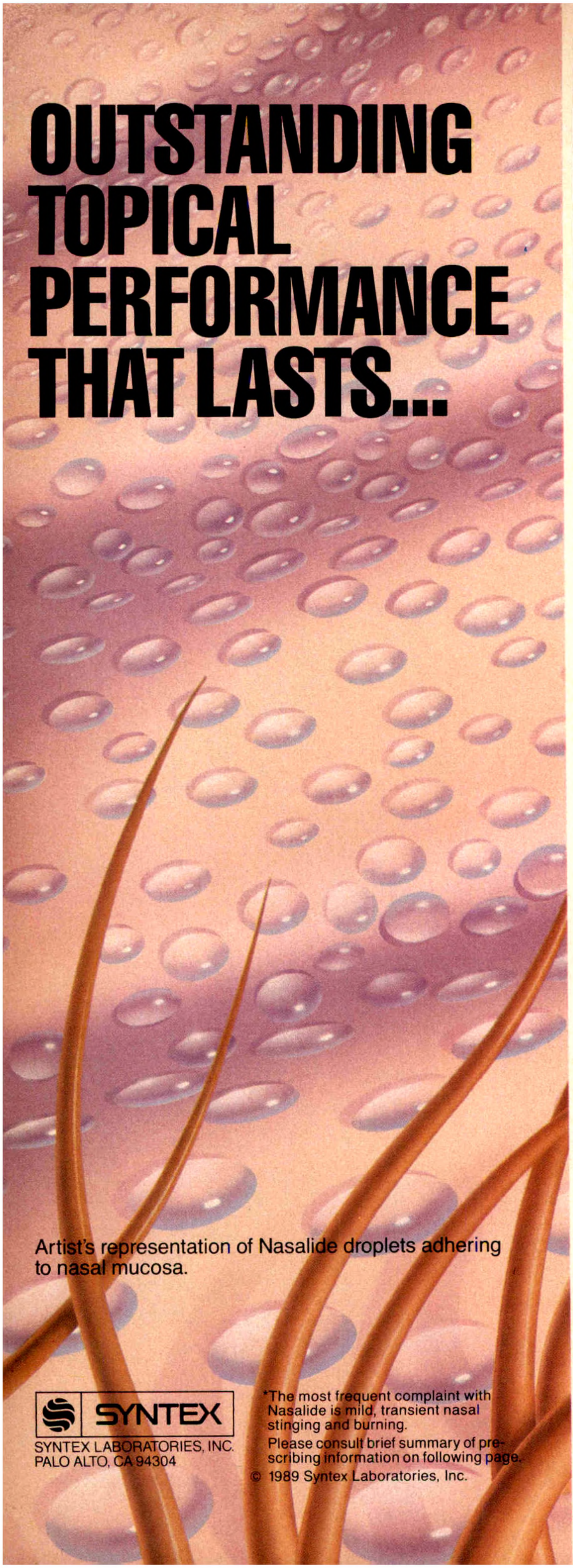

Artist's representation of Nasalide droplets adhering to nasal mucosa.

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OTHER PUBLICATIONS

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Transcripts of Panel Discussion, International Symposium on the Larynx, University of California, School of Medicine, San Francisco, California. 42pp. Softbound $15.00 U.S.

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Improvement is based on a local effect rather than systemic absorption. Improvement is usually apparent within a few days after starting Nasalide but may take as long as 2 weeks in some patients. Although systemic effects are minimal at recommended doses, Nasalide should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. Nasalide should not be used in the presence of untreated localized infection involving nasal mucosa.

Contraindications: Hypersensitivity to any ingredients.

Warnings: Patients transferred from systemic steroid therapy to Nasalide should be monitored to avoid acute adrenal insufficiency in response to stress. Since some patients may experience symptoms of withdrawal, attention must be given to patients previously treated for prolonged periods with systemic corticosteroids, particularly those with associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of symptoms. Nasalide should be used with caution in patients on alternate-day prednisone for any disease.

Precautions: General: Localized *Candida albicans* infections of the nose and pharynx occurred only rarely in clinical studies, but if such an infection presents, treatment with appropriate local therapy or discontinuation of Nasalide treatment may be required.

Flunisolide is absorbed into the circulation. Systemic effects have been minimal with recommended doses but larger doses should be avoided since excessive doses may suppress hypothalamic-pituitary-adrenal function.

Nasalide should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

In patients who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery, or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Information for Patients: Nasalide should be used as directed at the prescribed dosage. Nasal vasoconstrictors or oral antihistamines may be needed until the effects of Nasalide are fully manifested. The patient should follow the Patient Instructions carefully and should contact a physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs.

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Pregnancy: Pregnancy Category C. The drug has been shown to be teratogenic and fetotoxic in rabbits and rats. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because other corticosteroids are excreted in human milk, caution should be exercised when the drug is administered to nursing women.

Adverse Reactions: The most frequent complaints were mild transient nasal burning and stinging (reported in approximately 45% of patients). These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of these symptoms.

Incidence of 5% or less: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headaches and loss of sense of smell and taste. As is the case with other nasally inhaled corticosteroids, nasal septal perforations have been observed in rare instances.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism could occur.

Dosage and Administration: Full therapeutic benefit requires regular use and is usually evident within a few days, but up to 3 weeks may be required for some patients to achieve maximum benefit. Patients should use a decongestant and clear their nasal passages of secretions prior to use. Recommended starting dose in adults: 2 sprays in each nostril b.i.d. If needed, increase to 2 sprays t.i.d.

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Rev. July 1989

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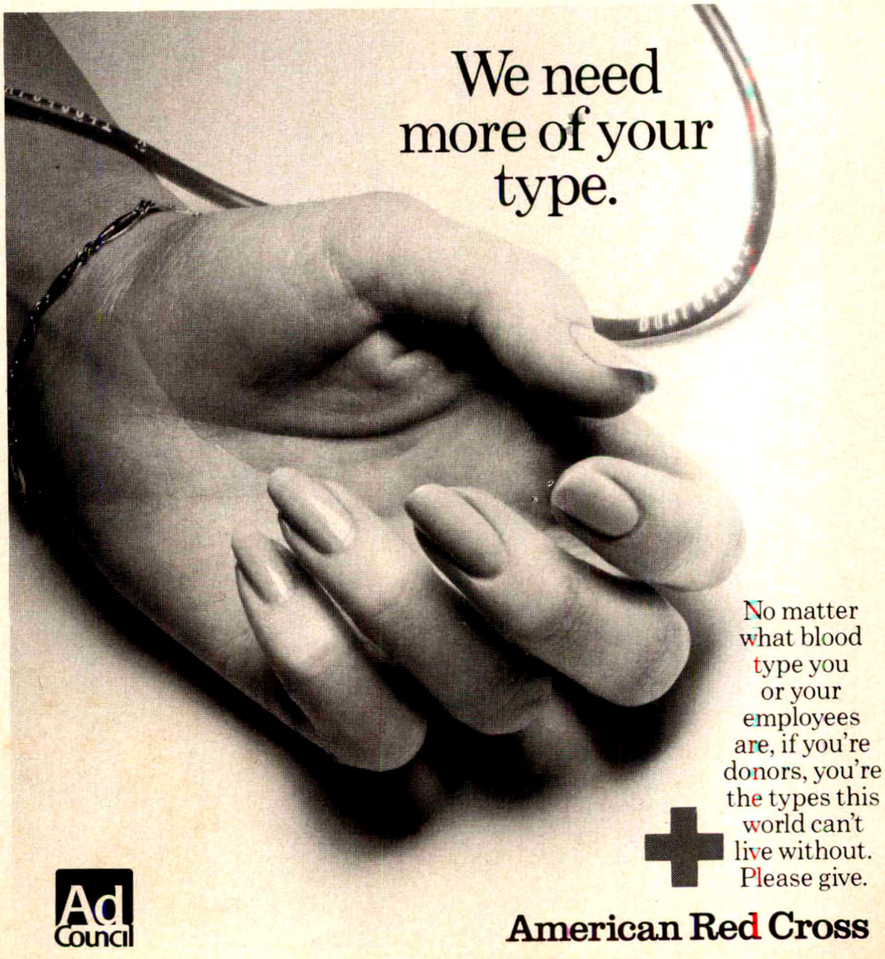
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Facial Plastic News

WAYNE F. LARRABEE, MD, SECTION EDITOR
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The Changing World of Medical Reimbursement

The changes occurring in the world of physician reimbursement are as earth-shaking in the practice of medicine as the San Francisco earthquake and, perhaps, as devastating.

To understand the havoc wreaked, a little background information would be helpful. Let us start with the different forms of physician compensation, which generally breaks down into three groups: fee for service (catch it while you can), discounted fees for service (rapidly rising in popularity), and capitation (still on the increase, but having problems).

Fee-for-service medicine is, of course, the preferred form of physician reimbursement and is the only form of payment generally used by physicians who practice cosmetic surgery exclusively. However, most members of the American Academy of Facial Plastic Reconstructive Surgery and/or American Association of Head Neck Surgeons, in addition to cosmetic surgery, also practice, to varying degrees, a broad spectrum of head and neck surgery. Because these services are frequently compensated at other than fee for service, it is important that we have an understanding of the other forms of reimbursement.

The traditional alternative (enemy) of fee for service is capitated medicine whereby the physician provides a continuum of health care services for a predetermined, prenegotiated set fee per patient per year. The Health Maintenance Organizations (HMOs), including those where physician's services are provided through Independent Physician Associations (IPAs), are the best examples of where this form of compensation is utilized. Although some may argue that this form of compensation lowers costs and leads to cost predictability, many others agree that under a capitation methodology, patient care frequently suffers. It has also been demonstrated that capitation medicine is not profitable and, in fact, many large HMOs are in serious financial difficulty.

The remaining payment scheme is discounted fee for service, a modified form of which is used to compensate physicians under Medicare. However, the major player using this form of physician compensation is the Preferred Provider Organization (PPO). As the name implies, PPOs essentially represent a group of selected providers (physicians, hospitals, etc.) offering services at some prearranged discount under terms of either an individual or group contract entered into with the major insurance companies or other payors. These discounts may take a variety of different forms. For example, one methodology uses a straight percentage of usual and customary rates (UCR) to determine compensation. This form tends to penalize physicians with the lowest fee profiles. Another methodology uses a geographic percentage discount where payment to all physicians in a particular community is made at the 90th percentile of the UCR prevailing for that geographic area. This form of payment can actually increase low-charge profile physicians. Varying combinations of both of these forms of payment may also be used.

However, the most popular discounted payment form used with PPOs is based on relative value systems (RVS). This methodology utilizes standard unit values that are intended to reflect inherent difficulties in procedures. To determine the discounted compensation level, these unit values are multiplied by a negotiated dollar factor. The most common of these systems in use today is the California RVS. Because this system was last revised in 1974, it is now under considerable criticism for not accurately comparing relative procedure difficulties and because newer procedures are not covered. Another RVS is McGraw-Hill, which attempts to consider certain geographic differences in their unit values and also factor in such items as time, skill, patient risk, and physician legal exposures. If this is now beginning to sound a little bit like the Harvard University Resource-based RVS (RBRVS) developed by Drs Hsiao and Braun, you are absolutely correct, since this newest unit value system is based in large part on its predecessors. The RBRVS system factors in the costs of running a practice, physical effort, time spent, technical skills, mental effort, judgment stress, geographic differences, and time in training. The RBRVS has been adopted by the Physician Payment Review Commission (PPRC), which advises Congress on payment reform. Congress, in turn, has passed legislation to utilize RBRVS in reimbursing physicians under Medicare. Further fine tuning of RBRVS is being done by a number of different groups including AMA's *Current Procedural Terminology* Editorial Board. *Current Procedural Terminology* is a comprehensive listing of descriptive terms that have become the most widely accepted nomenclature for reporting medical services. Because *Current Procedural Terminology* codes do not carry unit values, they cannot be used to determine physician charges and are, therefore, used in the billing process as descriptive modifiers only. However, it is these descriptions that will trigger the payment machinery of the RBRVS for Medicare and, eventually, most reimbursement packages. This Academy and the Association have representatives to the AMA's *Current Procedural Terminology* Editorial Board and the Association expends considerable time and effort advising in this area through its RVS Global Services Task Force.

It is incumbent on each member of the Academy to fully comprehend and use *Current Procedural Terminology* for coding and recognize the impact it can have on reimbursement. For example, an understanding of the subtle implications of *Current Procedure Terminology* office visit terminology can be critical. The concept of simple first and second office visit fees will no longer suffice. An appreciation of such concepts of extended, intermediate, or brief visits as opposed to consultations is also necessary, for their use will change reimbursement (but you'd better be ready to have whatever appropriate documentation is necessary to support them). In the surgical area, global fees are now becoming standardized and knowledge of how this will impact your compensation is critical (eg, what you may include in a laryngectomy may be seen as a separate service by others).

If what you have read so far does not have you concerned, then read on. First, remember that generally whatever Medicare does ultimately falls into the private sector; therefore, since they have adopted RBRVS, it is only a matter of time before insurance companies do the same. The ramifications, particularly for surgeons, could be devastating. Second, if you have not seen enough abbreviations, here are some more: *ICD-9* coding is a classification of disease entities that is used to establish the Diagnosis Related Groups (DRG) admitting diagnoses for hospitals. Not important to you? Yes they are, because DRG-based contracts for physician compensation are now beginning to appear in the PPO market. Contracts such as these, which base physician reimbursement on the disease rather than the complexity of the surgical procedure used to treat the disease, could prove to be disastrous. Nonetheless, the proliferation of such contracts in the future is very likely.

Hopefully, this article has answered some questions, stimulated a great deal more and, more importantly, provided you with some incentive to better understand the changes occurring in the systems used to compensate physicians. Better yet, hopefully, this article will cause you to become more actively involved in helping us to have some control over our own destinies.—DAVID A. BRAY, MD, Torrance, Calif.

In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Positron Emission Tomography
Eric M. Reiman, MD, Mark A. Mintun, MD (*Arch Intern Med*. 1990;150:729-731)

Clinical Review of Histamine 2 Receptor Antagonists
Robert J. Lipsy, PharmD; Brian Fennerty, MD; Timothy C. Fagan, MD (*Arch Intern Med*. 1990;150:745-751)

Serologic Tests for Lyme Disease
Steven W. Luger, MD, Elliot Krauss, MD (*Arch Intern Med*. 1990;150:761-763)

Thyroid Dysfunction of Adults Over Age 55 Years
Nandalal Bagchi, MD, PhD; Thomas R. Brown, PhD; Ronald F. Parish, JD (*Arch Intern Med*. 1990;150:785-787)

Clinical and Microbiological Evidence for Endemic Pharyngitis Among Adults due to Group C Streptococci
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Cocaine and Marijuana Use by Medical Students Before and During Medical School
Richard H. Schwartz, MD; David C. Lewis, MD; Norman G. Hoffmann, PhD; Nicholas Kyriazi, MD (*Arch Intern Med*. 1990;150:883-886)

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Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

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CONTRAINDICATIONS
Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS
Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS
General
Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients
Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions
Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C
Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use
Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS
The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE
Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION
Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

***Handling:** After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION
Federal law prohibits dispensing without prescription.

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C I B A

References:
1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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Other ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, methylcellulose, polygalacturonic acid, talc.

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Clinical Pharmacology RYNATAN combines the sympathomimetic decongestant effect of phenylephrine with the antihistaminic actions of chlorpheniramine and pyrilamine.

Indications and Usage RYNATAN is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications RYNATAN is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery while using this product.

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Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with RYNATAN. It is also not known whether RYNATAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RYNATAN should be given to a pregnant woman only if clearly needed.

Nursing mothers: RYNATAN should not be administered to a nursing woman.

Adverse Reactions Adverse effects associated with RYNATAN at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Overdosage *Signs and symptoms:* May vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment: Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration Administer the recommended dose every 12 hours.
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How Supplied RYNATAN® Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and 500 (NDC 0037-0713-96).

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Storage: RYNATAN® Tablets — Store at room temperature; avoid excessive heat — above 40°C (104°F).

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Editorial

Somehow We Have to Stop the Train Wreck

Part 1

We practice medicine in a reality that is changing and challenging. Many external forces are reshaping medicine in ways that we do not like, and the bad news is that the changes will intensify before they are completed. As physicians, we feel like the targets and the victims of many of these changes, and we must try to understand the driving forces behind them. To understand, we will examine the beliefs of the major groups that are reshaping medicine through their interaction. These differing *beliefs* underlie the decisions that are affecting all of us each day.

Doctors believe that health care is worth what it costs. We believe that health care will continue to improve and that it will continue to cost more. We believe that patients, government, and corporations need to understand the primacy of *quality* and need to bite the bullet in terms of reasonable cost.

Patients believe that health care is no longer a privilege, that it is a right. They also believe that there must be a way for them to obtain high-quality, low-cost, readily accessible health care.

Business believes that the process of utilization review is being gamed, and that the health care system is inefficient because physicians are poor managers. They also believe that money can be shifted within their corporate structure from health care costs to corporate profits, if they can rearrange the manner in which health care is provided.

Government believes that health care is an extremely important issue, because health care policy can win or lose votes for individual politicians. Government also believes that it can decrease its share of the cost of health care in the United States.

BELIEFS LEAD TO CONCLUSIONS

Based on the beliefs outlined above, each group has drawn a set of *conclusions* that are taking shape in the decisions that are being made currently and that are reflected in the impact these decisions are having. Let us look at these conclusions.

Doctors have concluded that patients want quality care at bargain rates but that only a few of these patients are serious about preventive medicine. Physicians have also concluded that the government is playing politics with the nation's health care system and that business and corporate interests are lobbying effectively to lower physician's fees (incomes) through direct physician employment (health maintenance organizations), fee discounting (paid provider organizations), and moves in the direction of a national health care system.

Patients have concluded that physicians charge too much, make them wait too long, and do not really care about them as an individual. They have also concluded that the government can design a system that will give them low-cost, easy-access, and high-quality medical care when they are old and/or out of work. The public has also concluded that business has an obligation to provide total health care benefits (which costs in excess of $2000 per capita per year) for no more than $200 per year out of their pockets (as an employee benefit).

Business has concluded that physicians are responsible for the increase that has occurred in health care costs and, as a result, that physicians are pushing industry into a zone of noncompetitiveness. Corporate America has also concluded that patients will overutilize any health care plan that can be provided and, therefore, that the government can and should solve the financial problems of business through the implementation of new forms of health care, such as the Canadian system.

Government appears to have concluded that physicians provide too much unnecessary care and are responsible for increased utilization of expensive services. Government has also concluded that patients are willing to accept a system such as the Canadian system or the Veterans Administration Hospital system and that business can serve a useful purpose as the catalyst for driving the shift to increased regulation and decreased reimbursement for health care.

THE VIEW FROM THE TRAINS

Imagine, if you will, four trains that are heading toward each other at high speed on intersecting tracks. We have the equivalent in the form of physicians, patients, business, and government, each group moving forcefully ahead on a track that seems destined to result in a catastrophic collision. What does the view look like from each of these trains?

From the patient train, the patients generally see things as being pretty much on track in terms of their basic health care needs, but they have certain fears in regard to catastrophic costs. We have noted in recent months that these fears are not great enough for them to wish to pay the costs of actual insurance coverage for catastrophic care. Things look pretty good for many passengers on the patient train if they have good coverage, low deductibles, and freedom of physician selection (available when it is "subsidized" to a considerable degree by the employer, who passes the cost along to the consumer). The concept of health care as a right appears to have taken deep root in our society, and the passengers on the patient train feel that they are entitled to ready access to all forms of new health care technology, regardless of the expense.

The view from the physician train is one in which patients are seen as resisting efforts to get them to *take more responsibility* for their own health and for their individual health care costs. Physicians do not understand how we can provide high-quality, easy-access, and low-cost health care all in one package. It is like the sign at the Chinese laundry that says "High quality, fast service, low price—pick any two of the above." No one seems to be taking this particular point of view very seriously, but it seems inevitable that the rules of common sense will eventually take priority over many of the other forces currently at work. For the first time in memory, many physicians are expressing feelings of alienation and disenchantment with medicine as a profession.

The view from the business train is that the movement to health maintenance organizations and paid provider organizations is *good*. Recall the line from the recent movie, "Wall Street," in which Michael Douglas makes an impassioned speech around the concept that "greed is good." There seems to be a correlation here. The political lobbying and the proliferation of health care brokers are also seen as good by business because, initially, they appear to drive down the costs of health care. The only problematic view from the business train is that the process is moving too slowly for them. They see health care as a commodity, like any other cost of doing business, and the less it costs, the better it is.

The view from the government train is one of guarded optimism as the passengers see that moving gradually is an effective strategy. They note that changing the reimbursement policies is changing the health care system in the direction they want to see it move. They also see that *increasing regulation* is changing the health care system in their preferred direction. But the problem with the view from the government train is that the horizon is only 1 to 2 years for long-range planning in government, and that translates to about 100 yards of visibility in a speeding train that is moving through the fog.

CURRENT PROBLEMS WE CAN SEE AND MEASURE

During the past few years, there have been quite a number of problems worthy of our interest. Any of you could prepare a different list and each of you could add to the list below, but the items that come readily to my mind include the following.

1. The catastrophic care fiasco showed us that taxpayers will not support the actual costs of the programs that they seek.
2. The problem with cost shifting, a strategy that has reached its limits, is that there are no more deep pockets to pick.
3. The perception that the doctor-patient relationship is becoming unraveled.
4. Numerous hospital closings have had an impact on the people these hospitals served. (Texas has lost 105 hospitals since 1980 and, in 1989, 15 hospitals closed, of which 11 were located in rural communities.)
5. Large teaching hospitals are in trouble, raising concerns about health care education and the future training of physicians.
6. Professional liability issues continue to change the way patients are treated (defensive medicine).
7. Litigation among and between physicians is on the rise, with allegations of conspiracy, conflict of interest, slander, and breach of contract becoming commonplace.
8. Failures of health care corporations are escalating because of the overselling of benefits, the aging of covered populations, and the impact of the acquired immunodeficiency syndrome and drug addiction along with regional economic slumps.
9. Patient dissatisfaction is growing as the public perceives adverse effects from gatekeepers, health maintenance organization financial reserves for care that is not provided, profit-driven diversion of patients to nonphysicians (eg, referral to optometrists rather than ophthalmologists), misleading advertising, and various forms of health care resource rationing.
10. Physicians are perceived by the public as spending more time and effort on their business and tax affairs, insurance, marketing, contracts, regulations, and negotiations than they do in the provision of medical care.
11. Indigent and underinsured and elderly patients are beginning to feel a squeeze as the states decrease their support of Medicaid and other programs in parallel with the federal squeeze on Medicare funds.
12. The acquired immunodeficiency syndrome, drug addiction, and thousands of very sick neonates constitute three epidemics for which there is no immediate or easy solution.
13. The media find it attractive to highlight malpractice issues, hospital scandals, and other events that detract from the professionalism of physicians, without devoting equivalent time to the outstanding programs that provide health care in most communities.
14. Health insurance costs continue to escalate and there appears to be no end in sight.
15. There continues to be a rush to find painless, quick fixes and to implement them, working from a horizon of 1 to 3 years instead of 20 to 30 years.

CONCLUSION

From this review of current beliefs, conclusions, and problems, we can see that all is not well within the house of Medicine. It has required a very complex set of events to bring us to our present position, and, while we have a great deal of which to be proud, we also must face the reality that there are problems with which we must deal.

Next month, the second part of this editorial will focus on future problems that are predictable and a set of solutions that may be useful in turning a couple of these trains into a different direction. No one wants to sit on the side of the hill and watch the train wreck occur. No one will benefit; everyone will lose if that is permitted to happen. I hope that this editorial will stimulate thought and action in a constructive direction.

Byron J. Bailey, MD
Chief Editor

Original Articles

Incision and Scar Analysis in Open (External) Rhinoplasty

Peter A. Adamson, MD, FRCSC; Oakley Smith, MD, FRCSC; Guy J. Tropper, MD, FRCSC

• Open (external) rhinoplasty is becoming increasingly popular. Two of its disadvantages most frequently espoused are the difficulty in making the external incision atraumatically and the resulting scar. To diminish these concerns, different incision lines and methods of exposure have been proposed by various authors. These are reviewed along with our preferred technique. We reviewed 100 consecutive cases of open rhinoplasty, yielding 81 patients who underwent subjective and objective scar analysis. There was 1 subjective failure (1.2%), and 2 minor objective failures (2.5%). Recommendations are made to minimize difficulties in performing the open approach and to maximize scar cosmesis.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:671-675)

In recent years, the popularity of open (external) rhinoplasty has steadily increased. This interest is evidenced by numerous articles discussing this technique in the literature.[1-6] Although some surgeons now prefer this method of exposure for virtually all their cases, polite but determined resistance to the technique is displayed by others. Many surgeons have no or limited experience with the open approach, and therefore restrict themselves to closed techniques. Still others have little knowledge of the concept of the procedure and are unable to assess the benefits it may offer to them. Thus open rhinoplasty may be perceived by some as a threat to the closed approach, and has resulted in a polarization of opinions that has sometimes hampered productive discussion. Although surgeons performing the open approach consistently emphasize the minimal scar, it is still the most frequently cited disadvantage of the technique. Other disadvantages cited include increased operating time, prolonged tip edema, and necessity to remove sutures.

MATERIALS AND METHODS

Approaches to Rhinoplasty

The rhinoplasty surgeon has a choice of several approaches to the nose. The approaches can conveniently be divided into open and closed techniques. They all contribute to a spectrum of varying exposures of the suprastructure of the nose. Generally speaking, the greater the amount of tip correction involved the more elaborate the surgical exposure needed.

Any given surgeon may prefer a different incisional approach either as a "routine" or for a specific problem. Transcartilaginous incisions have a restricted application, as it can be difficult to treat tip deformities accurately. The intercartilaginous incision alone may be used if minimal tip work is required, as it provides exposure exclusively to the dorsum unless a retrograde approach to the tip is also employed.

The most common method used presently is probably the cartilage delivery technique. By delivering the alar cartilages through marginal and intercartilaginous incisions, the major portion of the nasal base is exposed. However, mobilization of the cartilages from their anatomic position distorts their relationships and may impede proper diagnosis and management of deformities. It offers no additional dorsal exposure over other closed techniques.

Open rhinoplasty provides unparalleled and undistorted exposure of the nasal pyramid, tip, septum, columella, and anterior nasal spine. All surgical maneuvers, except lateral osteotomies, can be performed under direct vision. This allows precise resections as well as exact placement and suture fixation of grafts. No other method offers the panoramic exposure provided by the open approach. We are admittedly biased toward this technique. It is our contention that if the procedure allows more judicious and precise surgical manipulation of the "difficult" nose, it also offers potential for more controlled and superior results in less intimidating nasal deformities.

However, there are disadvantages inherent to the open approach that should be addressed.[7]

Operative Time

The open technique usually takes longer to perform than closed techniques.[8] This is due to two factors: (1) closure of the columellar incision; (2) greater appreciation of

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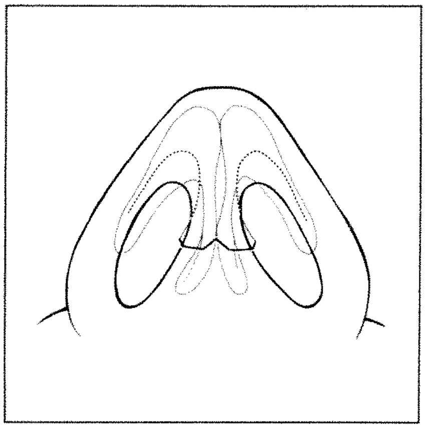

Fig 1.—Basal view: middle columellar gull-wing incision.

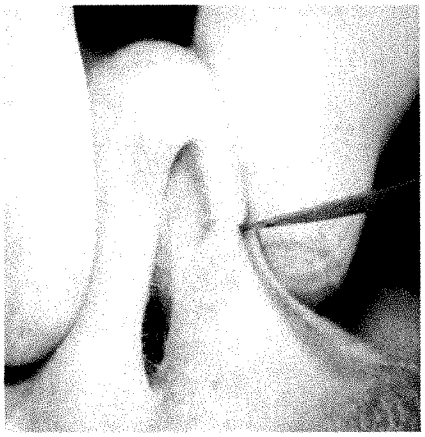

Fig 2.—A No. 11 blade "saws" columellar skin.

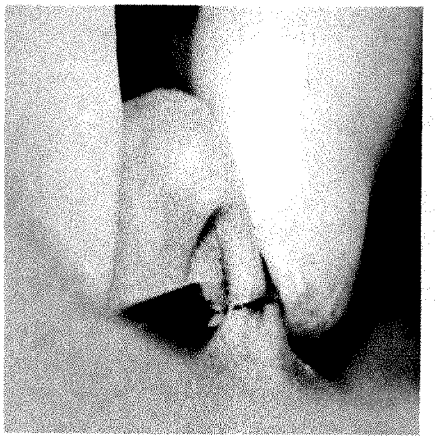

Fig 3.—A No. 15 blade incises vestibular skin.

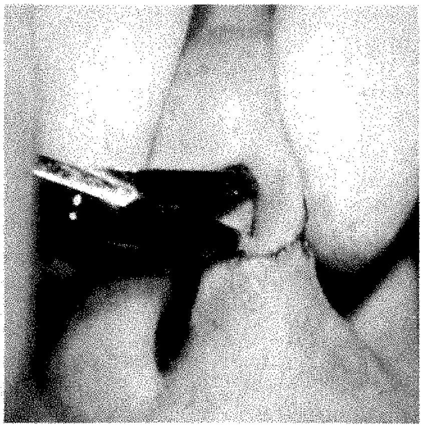

Fig 4.—Elevation of columellar flap with Converse scissors.

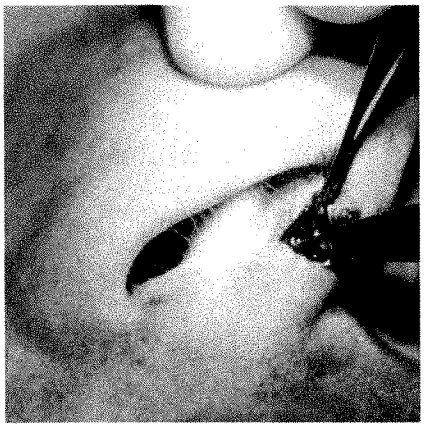

Fig 5.—Undermining lower columellar wound edge.

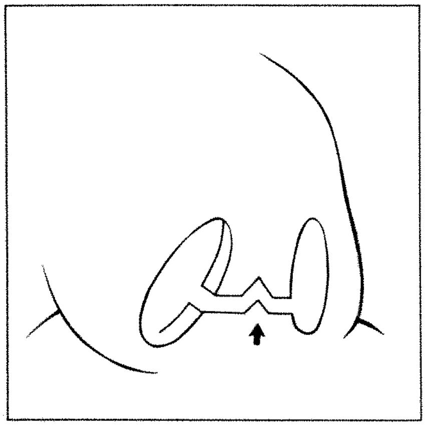

Fig 6.—Advancement of the lower edge of the columellar wound (when flap is too short).

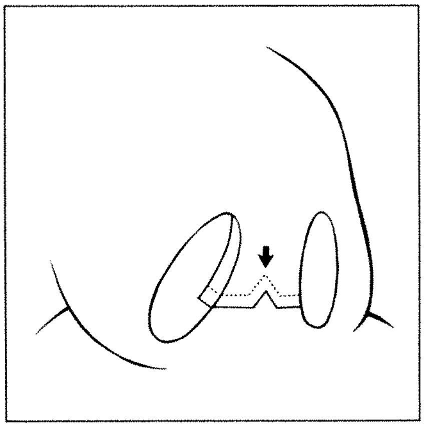

Fig 7.—Shortening of the columellar flap.

deformities leads the surgeon to more detailed reconstruction. As the surgeon becomes more adept with the open approach, the extra operating time can usually be reduced to approximately 15 to 20 minutes more than cartilage delivery techniques.

Postoperative Edema

Postoperative nasal base swelling is temporarily increased due to the time required to reestablish normal venous and lymphatic drainage of the tip, infratip lobule, and columella through the columellar incision. By 6 months, edema is usually minimal and comparable with that seen following endonasal techniques.[9] The additional edema theoretically might put the patient at higher risk of developing postoperative soft-tissue polly-beak deformity. However, it is our experience that if the supratip dead space is closed by placing a mucosal apposition transfixion suture high in the vestibule, the incidence of this complication is no higher than that associated with other rhinoplasty approaches. A review of cases by one of us (P.A.A.) in 1987[6] disclosed that 5 (3.2%) of 158 patients underwent revision surgery for polly-beak deformity. In only 1 of the patients (0.6%) was the deformity resulting from excessive soft-tissue formation. Hypesthesia of the tip also disappears from a few weeks to months.

Suture Removal

Postoperative care includes removal of nonabsorbable sutures. Fast-absorbing gut sutures minimize this necessity, but may cause some columellar inflammation.

Columellar Scar

The gull-wing columellar incision has repeatedly been mentioned as a major disadvantage[10] and a significant objection to the open approach. There is little literature analyzing the aesthetic impact of the scar or the incidence of wound complications. One wonders why the columellar scar raises such objections when lesions that leave more obvious scars are frequently removed from the face for cosmetic purposes. The columellar scar is similarly less visible than well-healed alar-facial groove scars that are accepted as being well tolerated. Figures 1 through 4 depict the technique of columellar incision and flap elevation. The transverse incision runs parallel to the re-

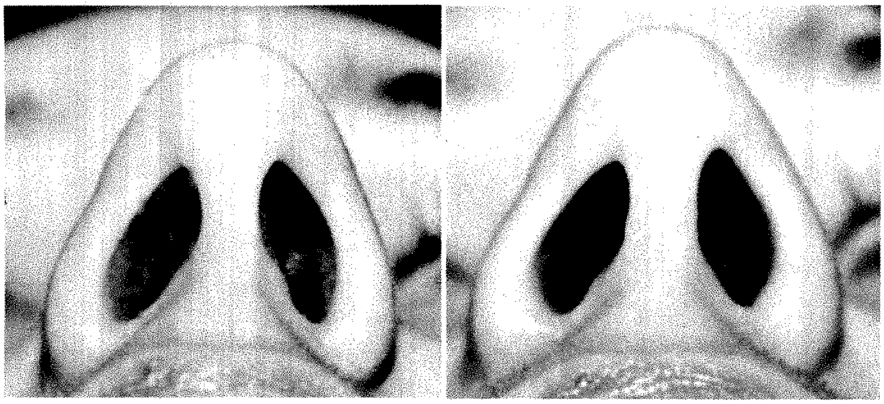

Fig 8.—White patient. Left, Preoperative. Right, 12 months postoperative.

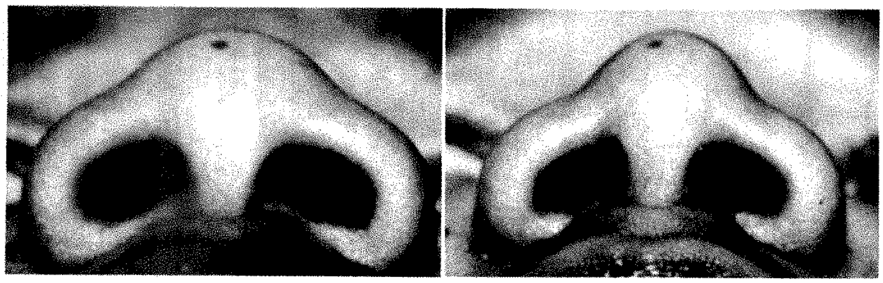

Fig 9.—Black patient. Left, Preoperative. Right, 6 months postoperative.

Patient Questionnaire

Are you conscious of the scar under your nose?
If conscious of the scar, do you use makeup to cover the scar?
If conscious of the scar, have you ever considered growing a moustache to camouflage it? (male patient)
Has anyone ever noticed your scar or commented about it?

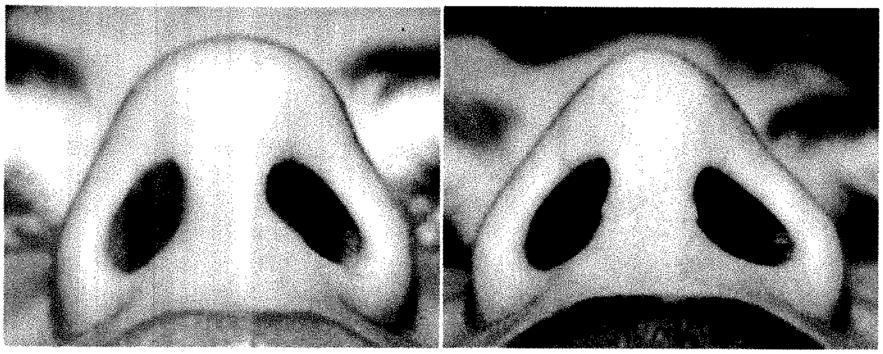

Fig 10.—Left, Preoperative. Right, 12 months postoperative; slight trap door effect.

laxed skin tension lines. The gull-wing portion breaks up the incision line visually and redistributes the wound's contractile forces. This reduces the risk of producing a depressed scar and notching of the columella. Placing of the "V" of the gull-wing in an inverted fashion rather than upright theoretically improves the flap vascularity. A simple columellar inverted "V" incision is longer, tends to widen more, and notch laterally. A staircase incision has a greater potential for asymmetry.

The columellar incision should not be placed below the medial crural feet, which may be especially short in blacks and Asians, as columellar notching may develop. Transverse scoring of the incision centrally and at right angles laterally allows more accurate reapproximation of the incision. The columellar incision is carried laterally around to, or just posterior to, the caudal margin of the medial crura, and from there extends in each vestibule as a marginal incision. No other endonasal incisions are necessary, thus avoiding the risk of vestibular stenosis that is sometimes seen with intercartilaginous incisions. Unfortunately, the vertical incision that connects the horizontal columellar incision to the lateral marginal incision runs not only perpendicular to the relaxed skin tension lines but also to the columellar incision itself. This creates a situation where the dynamics of wound healing may produce a trap door deformity at the junction of the two incisions. This is where the potential for scarring to produce deformity is greatest. This potential deformity is decreased by undermining the skin at this angle (Fig 5), thus allowing wound contraction to occur without contracture. A 5-0 nylon or 5-0 fast-absorbing gut simple suture is placed meticulously. No subcutaneous sutures are necessary. Finesse is required in closing the wound edges where they are of different thickness and at the incision angles. Columellar sutures are removed at 4 days, and the incision is taped. Corner sutures are left in place for 7 days.

Flap necrosis has been cited as a complication, but has fortunately remained only a potential one in our experience. In the few cases reported in the literature,[10] it appears to have resulted from errors in surgical technique. Wound dehiscence has been mentioned and theoretically is more likely to occur in cases of augmentation rhinoplasty, since the skin is being closed under more tension. This risk can be decreased by creating an advancement flap of the inferior columella before closure (Fig 6). In cases of large tip reductions, there may be a tendency for the redundant columellar skin to form a hanging columella. This 1- or 2-mm excess skin can be excised before closure (Fig 7). The columellar incision otherwise shares the same infrequent but possible complications common to any surgical incision.

RESULTS

One hundred consecutive cosmetic open rhinoplasty patients were reviewed. This yielded 81 patients who entered the study. All patients were from the practice of one of us (P.A.A.) and had a minimum follow-up of 6 months. Both objective and subjective assessments of the resulting columellar scar were performed.

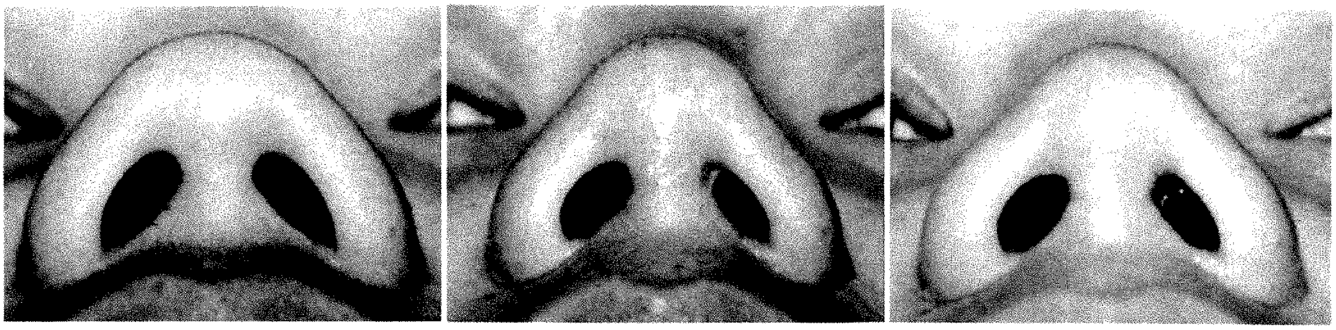

Fig 11.—Left, Preoperative. Center, 6 months postoperative; webbing at left superior columella. Right, 1 month after Z-plasty for correction of webbing.

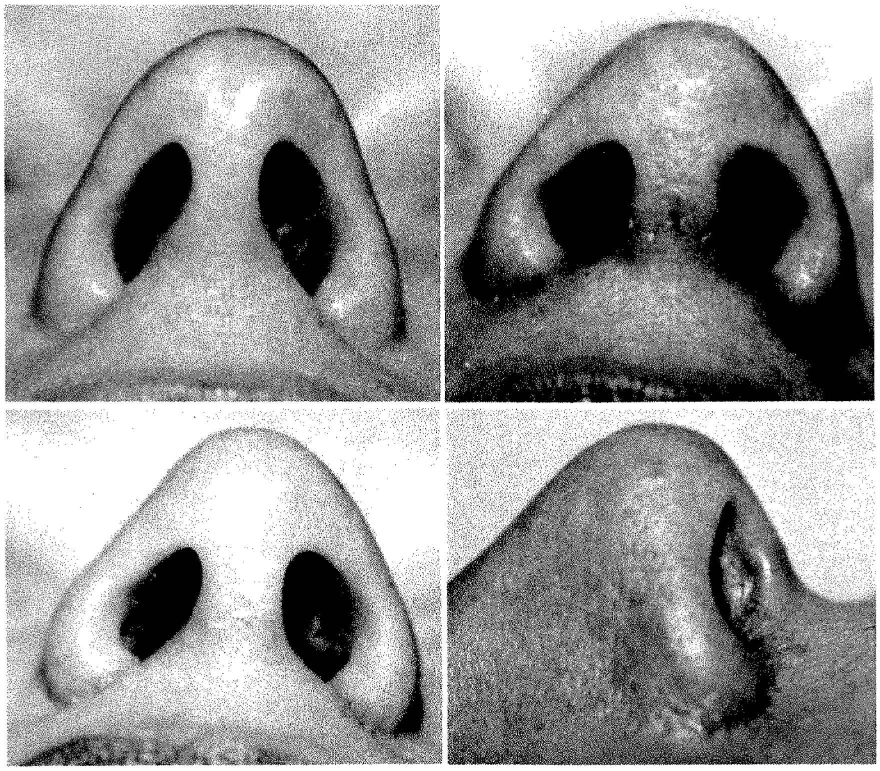

Fig 12.—Top left, Preoperative. Top right, Postoperative day 7. Bottom left, Postoperative day 21, basal view. Bottom right, Postoperative day 21, side view.

The 6-, 9-, and 12-month postoperative appointment and the 6- and 12-month basal view photographs were compared with the preoperative pictures and served as the basis of the objective analysis. An unsatisfactory result was considered present if anything other than a barely visible, level, and thin line scar without notching or tissue bunching was evident (Figs 8 and 9). Essentially anything less than a perfect cosmetic scar was deemed a failure.

The subjective analysis consisted of the questions in the Table. It was constructed in an attempt to study the impact the columellar scar has on the patient's own facial image and to ascertain how perceptible the scar is to the general public.

There were two objective failures representing a 2.5% complication rate. These were both minor. One patient (Fig 10) was found to have a trap door deformity located at the junction of the rim and columellar incision. The patient was unaware of the complication and has declined correction. Another patient (Fig 11) developed a web at the superior columella due to early suture loss and wound dehiscence—this could occur as easily with any marginal incision. This was corrected with a Z-plasty. Up to 7-year follow-ups show no significant change in the appearance of the scar occurring after 1 year.

There was one subjective failure, the patient with the superior web. For all others, the scar was essentially unnoticeable, and no one was self-consciously aware of the scar. No patient felt required to camouflage the scar by make-up or a moustache.

It is well appreciated by cosmetic facial surgeons that these patients are very demanding, and their level of expectation is higher than noncosmetic patients. Therefore, it is extremely likely that these patients would have complained if they felt the columellar scar was objectionable. Other surgeons have had similar experiences.[4,11] The incision has been used on models and performers as well with alacrity. We have no hesitation in recommending the open approach even in the case of dentists, dental hygienists, or other individuals who, because of their profession are more likely to be observed from the base. We have not had problems of aberrant healing of the columellar incision in black and Asian patients. Figure 12 illustrates the usual course of scar healing.

The columellar scar following open rhinoplasty is extremely well accepted, usually being of no concern whatsoever. The risk of complications arising from the incision is almost negligible if attention is paid to proper skin handling and wound closure techniques. Thus, the scar should not be a factor influencing the choice of approach to rhinoplasty.

The art of rhinoplasty lies partly in the diversity of ways to effect the desired modifications. One must emphasize the open technique is merely an *approach* to the nose, and that well-recognized bone, cartilage, and soft-tissue sculpting techniques must be applied to achieve the desired results. Personal experience and preferences will continue to guide the choice of approach to rhinoplasty. We believe it is unjustified to denigrate the open approach on the basis of the columellar scar. Surgeons should make a point to familiarize themselves with the open approach technique so as to include it in their "armamentarium." This means that teaching of open rhinoplasty should be part of every residency training program. Assuming a knowledge of sculpting techniques, we believe the improved exposure enables rhinoplasty surgeons to achieve more predictable and better results with fewer number of cases.

We currently use the open approach for all cases except those where we are satisfied that all nasal deformities can be diagnosed preoperatively and corrected satisfactorily with a closed approach.[6]

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

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Marshall B. Kapp, JD, MPH (*Arch Intern Med.* 1990;150:496)

Reliability and Validity of an Objective Structured Clinical Examination for Assessing the Clinical Performance of Residents
Emil R. Petrusa, PhD; Thomas A. Blackwell, MD; Michael A. Ainsworth, MD (*Arch Intern Med.* 1990;150:573-577)

Snoring in a Hispanic-American Population
Wolfgang W. Schmidt-Nowara, MD; David B. Coultas, MD; Charles Wiggins, MSPH; Betty Eberle Skipper, PhD; Jonathan M. Samet, MD (*Arch Intern Med.* 1990;150:597-601)

Evaluation of Patient, Physician, Nurse, and Family Attitudes Toward Do Not Resuscitate Orders
Cynthia J. Stolman, PhD; John J. Gregory, MD; Dorothea Dunn, RN, MS; Jeffrey L. Levine, PhD; (*Arch Intern Med.* 1990;150:653-658)

Demineralized Bone

Implant Resorption With Long-term Follow-up

Dean M. Toriumi, MD; Wayne F. Larrabee, Jr, MD; Joseph W. Walike, MD;
Donna J. Millay, MD; David W. Eisele, MD

• The osteoinductive properties of demineralized bone have stimulated its use in facial skeletal augmentation and reconstruction. Demineralized bone has been shown to induce phenotypic conversion of mesenchymal cells into osteoblasts, with bone formation within 29 days (osteoinduction). In this clinical study, 75 demineralized bone implants were followed up from 1 to 48 months (average follow-up, 14.3 months). There were 41 major dorsal implants, with an average degree of resorption of 50.7%. Eight dorsal implants were followed up for more than 24 months, with an 82.5% degree of resorption. Overall resorption for all implants was 49%. Major factors contributing to implant resorption included lack of surrounding mesenchymal cells and inadequate contact between host tissue and bone-inducing surface area. Other factors included infection, poor vascularity, and compression of the implant. Demineralized bone has an unacceptably high resorption rate and should only be used in highly selective cases where the implant can be positioned in a site rich in primitive mesenchymal or bone-forming cells.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:676-680)

Autogenous cartilage and bone are the preferred grafting materials for facial skeletal augmentation or reconstruction. However, donor site morbidity, limited quantities in certain cases, and unpredictable implant resorption have forced the surgeon to seek out different implant materials. Alloplastic materials such as Proplast, silicone rubber, and Silastic have all been used as implants. All of these materials act as a foreign body with differing degrees of tissue reaction. These materials are not biologically incorporated into host tissue and are susceptible to resorption of adjacent bone or infection.

In 1965, Urist[1] showed that demineralized bone induced bone formation. Reddi and Huggins[2] demonstrated that demineralized bone powder had increased bone matrix surface area that allowed formation of discrete transformation plaques within 24 hours. Banked undemineralized allogeneic bone undergoes slow resorption and ingrowth of low-density new bone from the margins of the defect over periods of months to years (osteoconduction).[3] Demineralized bone induces phenotypic conversion of mesenchymal cells into osteoblasts, with high-density bone formation in 14 to 29 days (osteoinduction).

Demineralized bone is cadaver bone that is demineralized with hydrochloric acid, sterilized with gamma irradiation using cobalt 60, freeze-dried, and packaged. The implants come in many forms including whole and split rib, sectioned fibula, femoral head or trochanter, cancellous chips, crushed cortical chips, and cortical powder. Demineralized bone is easily carved and molded, well tolerated, and sold at a reasonable cost.

The bone-inducing properties of demineralized bone occur via an inductive, not a conductive, process. Therefore, bone formation requires adequate contact between host tissue and the demineralized bone implant. Several other factors may act to determine the rate of implant resorption. Presently, to our knowledge, there are no long-term clinical studies evaluating the rate of resorption of demineralized bone implants used for facial augmentation. In this clinical study, demineralized bone implants used for facial augmentation or reconstruction were followed up for an extended period to evaluate degree of implant resorption. Factors such as size, shape, and location of the implants were also evaluated.

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Demineralized Bone Implants

Location/Use of Implant	No. of Implants	Follow-up, mo		Average Degree of Resorption, %
		Average	Range	
Augmentation nasal dorsum	41	13.0	1-48	51
Small dorsal nasal defects	10	15.3	1-36	20
Columella	19	16.4	1-36	22
Nasal tip	3	20.7	3-37	73
Malar	1	36.0	. . .	30
Chin	1	26.0	. . .	20
Total	**75**	14.3	1-48	49

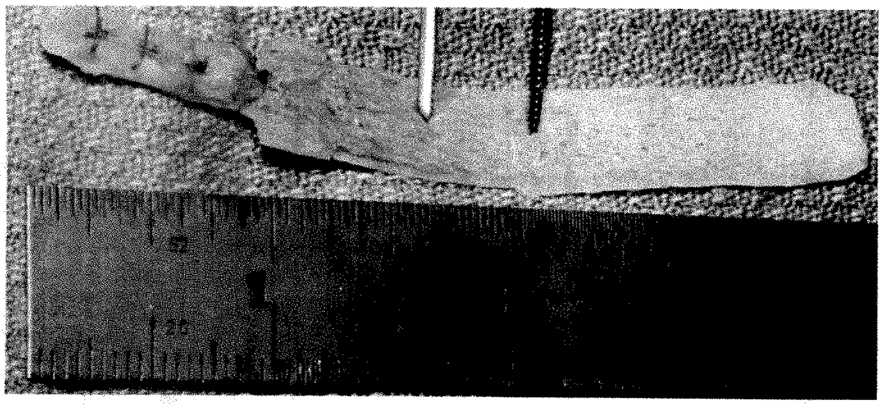

Fig 1.—Combination dorsal/columellar implant to augment dorsum and to add bulk and support to the medial crural/columellar complex.

PATIENTS AND METHODS

Between 1985 and 1989, 53 patients underwent facial reconstruction using allogeneic demineralized bone implants. Revision procedures or multiple implant sites were each counted as a separate implant (75 total implants). Revision implants were included because the indications for, and the site and technique of, implantation were similar to those for primary implants. Demineralized split rib, bone chips, or cortical powder was obtained from the same commercial source (Mile High Transplant Bank, Denver, Colo). The majority of the implants were used for correction of nasal deformities (saddle nose, dorsal nasal irregularities, and columellar defects). The Table shows the location of the implants.

The implants were hydrated in saline and prepared for implantation. Split rib was carved or layered to the appropriate size and shape (Fig 1). Chips or powder was carefully hydrated and packed into position. All implants were positioned through either an intranasal or an open (external) rhinoplasty approach (Figs 2 and 3). Whenever possible, the implants were sutured into position with absorbable suture. In many cases, multiple-layered (laminated) implants were used to augment the nasal dorsum or as a premaxillary plumping graft.

In each case, standard preoperative photographs were taken prior to any attempt at reconstruction. In most cases, initial postoperative photographs were obtained within 2 months after surgery. These early postoperative photographs were taken to record the maximal degree of augmentation. To facilitate comparison, all photographs were taken using the same technique and photographic settings. Patients were followed up for a period ranging from 1 to 48 months. In many cases, several sets of postoperative photographs were taken to document any gradual changes that may have taken place.

POSTOPERATIVE EVALUATION

The degree of resorption of each demineralized bone implant was evaluated using clinical parameters. Implant resorption was described as complete (80% to 100%), near complete (60% to 80%), moderate (40% to 60%), partial (20% to 40%), and minimal (0% to 20%). These determinations were made by comparing early postoperative photographs with the most recent postoperative photographs. Degree of resorption was defined as the amount of implant resorption noted at the time of the last clinical evaluation.

Prior studies with two-dimensional facial analysis demonstrate that profile analysis of facial structures from photographs can provide accurate comparative data on midline facial structures (such as the nose).[4]

RESULTS

Fifty-three patients underwent facial augmentation or reconstruction using demineralized bone implants, with follow-up ranging from 1 to 48 months (average follow-up, 14.3 months). The Table shows the distribution of the implants. Most of the implants were used to correct deformities of the nasal dorsum and columella. Ten patients underwent implantation of a small piece of demineralized split rib or bone chips to fill in small depressions along the nasal dorsum, with an average resorption of 20% (average follow-up, 15.3 months). Nineteen columellar implants were performed, with an average resorption of 22% (average follow-up, 16.4 months). A total of 41 major dorsal implants were utilized, with an average resorption of 50.7% (average follow-up, 13 months). There was 67% resorption with "first-time" implants (initial procedure). When a secondary procedure was performed adding additional demineralized bone to the dorsum, the degree of resorption dropped to 42%. However, in most of the secondary procedures only a single layer of demineralized split rib was used. Nineteen dorsal implants were followed up for greater than 12 months, with a degree of resorption of 64.2%. Eight dorsal implants were followed up for more than 24 months, with a degree of resorption of 82.5%.

Of the nine patients who underwent multiple procedures because of implant resorption, six did well (less than 40% resorption) after demineralized split rib was added a second or third time. In most cases, the amount of implant resorption decreased with each subsequent implantation. However, the size of the implant also decreased with each subsequent implantation.

When demineralized split rib was used in the nasal tip region to add projection, lack of rigidity and implant resorption eventually resulted in loss of tip projection (Fig 4). There was

73% resorption for nasal tip graft implants after an average follow-up of 20.7 months.

In one patient, demineralized split rib (laminated) was used as a malar implant. After 7 months, partial resorption of the implant was noted.

Of the 41 implants used for major dorsal augmentation, 13 (32%) totally resorbed (Fig 5). At least 17 of the major dorsal implants were multilayered or laminated. These implants had two, sometimes three, layers of demineralized split rib sandwiched together to provide more bulk. The average degree of resorption of these implants was 69% (average follow-up, 12.6 months).

The overall degree of resorption for all implants was 49% after an average follow-up period of 15 months (range, 1 to 48 months).

In two cases, too much demineralized bone was implanted, requiring a secondary procedure to remove the excess implant tissue. In one case, histologic examination of the tissue revealed osteoid material consistent with bone, showing some focal calcification. In the other case, histologic examination revealed fibrosis with a few islands of cartilage but no bone.

In this series, there were two documented infections with complete resorption of the implant.

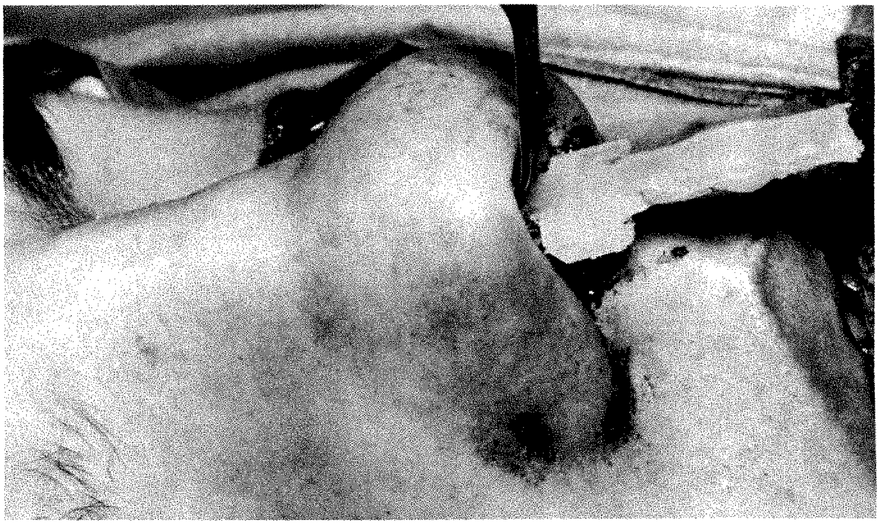

Fig 2.—Combination dorsal/columellar implant being inserted via a marginal incision.

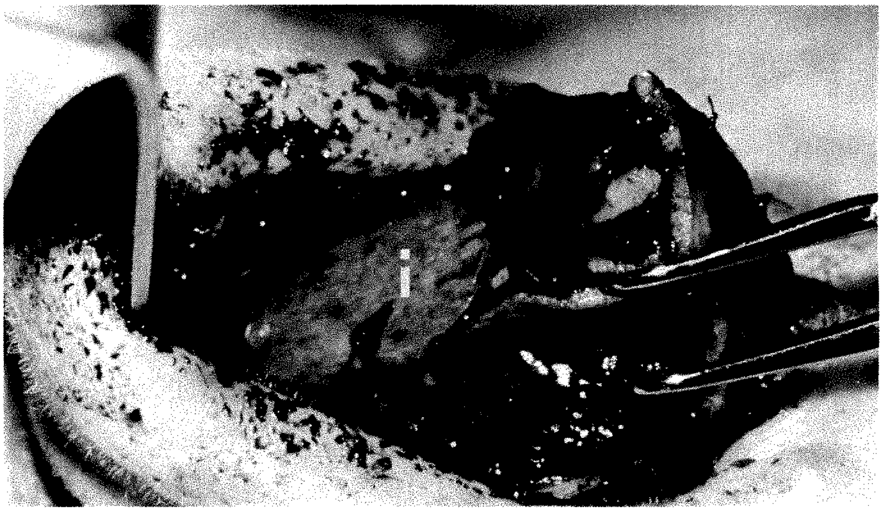

Fig 3.—Dorsal graft placed over the dorsum via the open rhinoplasty approach. Sutured-in-place dorsal implant (i).

COMMENT

Early animal studies revealed that hydrochloric acid-decalcified (demineralized) bone possessed impressive bone-inductive properties.[1,2,5,6] However, there are relatively few clinical studies that effectively evaluate the long-term resorption of these implants. In 1981, Glowacki et al[7] used demineralized bone implants for craniofacial reconstruction in 34 patients, 28 with congenital defects and 6 with acquired defects. In their early follow-up, they found rapid union, healing of large defects, avoidance of harvesting procedures, and the potential for an unlimited supply of implant material. Biopsies performed on several patients revealed new bone formation. They believed that bone formation occurred via bone induction rather than via bone conduction.

Mulliken et al[8] used demineralized bone to reconstruct craniofacial defects in 42 patients. They used demineralized bone implants in three forms: blocks, chips, and powder. Bone formation was evaluated by clinical and roentgenographic examination. Of the sites suitable for complete evaluation, 31 of 35 were completely healed within 3 months. Implant resorption occurred in 4 patients, 3 with a corticocancellous implant and 1 with a demineralized bone powder implant. Mulliken and Glowacki[9] believed that demineralized bone powder was the superior implant, because it exposed the greatest surface area of host tissue to bone-inducing surface area. In another study, Mulliken[10] found that dense cortical demineralized bone implants used for nasal reconstruction failed to induce sufficient bone formation to maintain the desired nasal contour. Moderate (approximately 50%) late implant resorption occurred in most of their cases.

Ousterhout[11] reviewed 25 patients who underwent augmentation or reconstruction of the craniofacial region with demineralized bone. In this study, patients were followed up for 16 to 18 months. More bone formed when demineralized bone powder was used instead of a solid cortical bone implant. Compared with the cancellous bone implant, cortical bone offered rela-

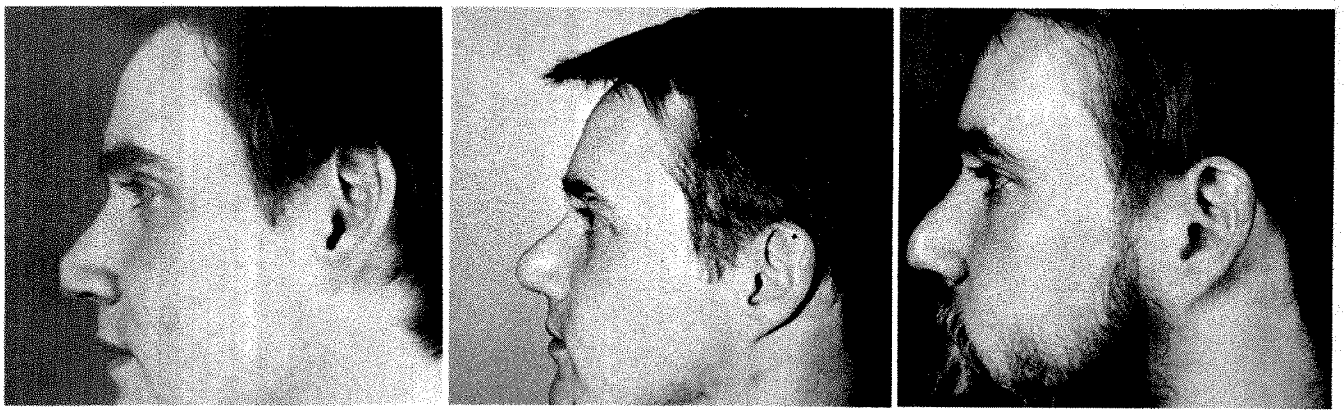

Fig 4.—Demineralized split rib used as a combination dorsal/nasal tip/columellar implant to provide support and tip projection. Left, Preoperative lateral view showing tip ptosis. Center, Modest increase in tip projection 4 months postoperatively. Right, Near complete resorption of implant at 39 months.

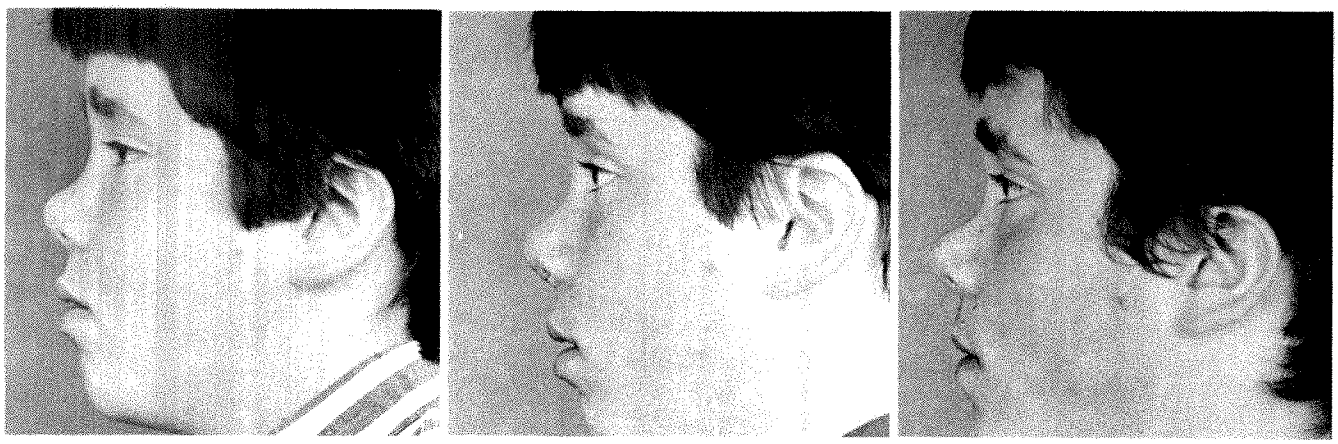

Fig 5.—Large dorsal nasal implant. Left, Preoperative lateral view demonstrating severe saddle nose deformity in a patient with a history of nasal trauma. Center, Modest improvement of dorsal nasal profile 1 month after augmentation of the dorsum with a large demineralized split rib implant (laminated). Right, After 2 years of follow-up, a significant amount of implant resorption has already occurred.

tively little surface area for bone induction. When filling a bony defect, the implant seemed to work better, with good bone formation. When demineralized bone was used for augmentation (in the nasal dorsum, chin, and malar region), the implants demonstrated a greater degree of resorption.

In this study, we reviewed patients who underwent primarily dorsal nasal augmentation using demineralized split rib implants. Many of these patients had saddle nose deformities (congenital or iatrogenic). With most implants, there was 40% to 60% implant resorption after a follow-up period of 1 to 48 months. Major dorsal implants had a 50.7% degree of resorption, with total resorption of 13 implants. In laminated implants, split rib grafts were sandwiched together, decreasing host tissue contact, hindering bone induction, and increasing resorption. Even though the average degree of resorption for major dorsal implants was 50.7%, implant resorption appeared to increase as the follow-up period was extended. Long-term follow-up of large nasal implants showed an 82.5% resorption at greater than 24 months. Longer follow-up may reveal even greater degrees of implant resorption. Nasal tip implants also did poorly (73% resorption), which may be partly due to the lack of rigidity of these implants and their inability to provide tip projection.

On the other hand, small pieces of demineralized bone used for small dorsal irregularities or for adding bulk to the columella held up well, possibly because of improved host tissue contact. As a columellar strut, split rib can provide bulk but does not add much support.

Selected patients underwent secondary procedures to add more demineralized bone based on their concern with the appearance of the deformity. When additional demineralized bone was implanted in a secondary procedure because of initial implant resorption, there tended to be less resorption of the second implant. This may have been a result of the old implant bed becoming occupied by some viable bone-forming cells that could be readily stimulated to form bone in the presence of an additional implant of demineralized split rib. However, our impression is that improved augmentation with secondary procedures is due to the fact that smaller implants were required. When smaller implants resorb, scar tissue ingrowth can more readily occupy the volume of the resorbed implant. Therefore, with each revisional augmentation the surgeon may have just been adding more scar tissue.

The major problem with using allogeneic demineralized bone for nasal augmentation or reconstruction is its variable degree of implant resorption. Even though the demineralized bone was obtained from the same commercial source, different degrees of implant resorption may be caused by variability in the preparation (decalcification or sterilization) of the demineralized bone. Furthermore, some degree of implant resorption may result from pressure of the tented skin overlying the projecting surface of the implant. This inherent compression may act to deform, erode, and increase implant resorption. The majority of the resorption is likely caused by (1) inadequate contact between host tissue and bone-inducing surface area and (2) inadequate bone-inducing activity present within the implant itself. Bone-inducing activity does not diffuse over a large area and therefore requires organic contact between host tissue and implant. This may explain why laminated implants (multiple layers) used for major dorsal augmentation, which oppose large areas of implants, did so poorly and resulted in excessive resorption (69%). Bone chips and powder had less resorption because of greater host tissue surface area contact. Other factors that may influence implant resorption include acute inflammation, immune response due to poor HLA match between host and donor, poor vascularity, and lack of local mesenchymal cells (bone, muscle, etc).

CONCLUSIONS

Demineralized bone is far from an ideal implant material; however, it can be effective if used properly in certain situations (craniofacial reconstruction, or when implanted in fresh bony defects). Demineralized bone chips or powder can be used to fill in small dorsal nasal defects. Demineralized split rib can be used to add bulk to the columella or premaxillary region but lacks support and should not be used to increase nasal tip projection. Demineralized bone seems to be more effective when implanted adjacent to viable bone or muscle. The presence of local mesenchymal cells may be a critical factor in the bone induction process of these implants. Demineralized bone is easy to use and avoids a tissue harvesting procedure; however, high resorption rates limit its use for nasal or facial augmentation. As reflected in this clinical study, one of the major uses for this implant material in facial plastic surgery would be for augmentation of the nasal dorsum. However, use of demineralized bone for this purpose is associated with a very high degree of resorption. The results of this study suggest that longer-term follow-up will result in even higher implant resorption rates. Any implant with a resorption rate greater than 60% to 70% is not going to be acceptable to most facial plastic surgeons.

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In Other AMA Journals

ARCHIVES OF SURGERY

Cost, Quality, and the Volume of Surgical Oncology Procedures
Eric Munoz, MD, MBA; Katherine Mulloy, AS; Jonathan Goldstein, MPA; Neol Tenebaum, MD; Leslie Wise, MD (*Arch Surg.* 1990;125:360-363)

Intraoperative Radiation Therapy and Hyperthermia: Morbidity and Mortality From This Combined Treatment Modality for Unresectable Intra-abdominal Carcinomas
Thomas A. Colacchio, MD; Christopher Coughlin, MD; James Taylor, MD; Evan Douple, PhD; Thomas Ryan, MS; Robert W. Crichlow, MD (*Arch Surg.* 1990;125:370-375)

Concentration of Salicylate in Serum and Perilymph of the Chinchilla

Flint A. Boettcher, PhD; Brian R. Bancroft, MA; Richard J. Salvi, PhD

• The concentration of salicylate in serum and perilymph was measured in chinchillas after intraperitoneal administration of sodium salicylate. Serum salicylate concentration peaked 2 to 4 hours after a single injection. Clearance was approximately complete after 16 hours. The within-subject variability of serum concentration 4 hours after injection was very low. Subject weight significantly affected serum salicylate concentration, with heavier animals showing higher serum levels. The relationship of perilymph to serum salicylate concentration was approximately linear, with a high correlation between measures.

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The salicylates, such as aspirin, are the most commonly used drugs in industrial societies. They are used for their anti-inflammatory, analgesic, antipyretic, and antithrombotic properties.[1] Many studies have suggested that in moderate to high doses, salicylates may cause mild to moderate hearing loss and tinnitus, both of which are reversible after termination of drug administration.[2-4] While the mechanism of salicylate ototoxic effects is not completely understood, the drug appears to act in the cochlea.[5-10] Recent studies have suggested that the site of action of salicylates is the outer hair cell.[8-10] Salicylates are reemerging as drugs of interest to hearing scientists since they may be used as a model of reversible hearing loss and tinnitus and may be useful in understanding better the role of the outer hair cell in hearing. This project examined salicylate pharmacodynamics in the chinchilla, a popular species for studying the changes in hearing brought about by ototoxic drugs, such as salicylates.

To understand the ototoxic effects of salicylates, investigators have attempted to relate serum and perilymph levels of salicylate with hearing loss and tinnitus. Myers and Bernstein[3] reported that the hearing loss caused by salicylate administration was better correlated with the serum salicylate level than with the oral or injected dose of the drug. In humans and monkeys, serum salicylate levels of 1.45 to 3.12 mmol/L (20 to 50 mg%) resulted in hearing losses of up to 30 dB.[3] The correlation between serum level and hearing loss 24 hours after injection was .88 in monkeys; hearing loss reached an asymptote and did not increase with serum levels greater than 2.50 mmol/L (40 mg%). Woodford et al[11] reported a median (N = 3) serum level of 4.08 mmol/L (65.3 mg%) and a range of 3.18 to 4.87 mmol/L (51 to 78 mg%) 3 hours after an intramuscular injection of sodium salicylate (400 mg/kg) in the chinchilla. Woodford and associates' subjects had a median hearing loss 3 hours after injection of 20 dB at 8 kHz and 10 dB at lower frequencies.

These examples demonstrate that there are species differences in the relationship of hearing loss to serum levels, since the chinchilla data revealed mild threshold shifts and high serum levels (>2.50 mmol/L [>40 mg%]), whereas the primate data showed moderate threshold shifts with serum levels less than 2.50 mmol/L (<40 mg%). In addition, the time course of hearing loss appears to be different across species. Thus, the first goal of this project was to determine the time course of serum salicylate levels in the chinchilla, to compare the ototoxic effect of the drug with the effect in other species. Preliminary data on the uptake of salicylate in the chinchilla was reported by Juhn et al,[12] although they did not describe the number of subjects or degree of hearing loss in their study.

Recent studies in our laboratory on the ototoxic effect of salicylates have suggested a high degree of variability of effect within subjects.[13] Hearing levels were monitored electrophysiologically, using the threshold of the evoked response recorded from the inferior colliculus. Subjects were tested 4 hours after an injection of either 300 or 450 mg/kg of sodium salicylate. Hearing loss in several chinchillas ranged from 0 to 30 dB on different test days, despite similar doses and test times after injection. To determine if the within-subject variability may have been caused by variable uptake of salicylate, serum levels were tested three times in each of three subjects, 4 hours after an injection of 450 mg/kg of salicylate.

One drawback to studying simply the relationship of salicylate dose to serum levels is that the investigator cannot be assured that the drug is incorporated into the cochlea. Previous work by Jastreboff et al[14] showed a close relationship between perilymph and serum salicylate concentrations in rats. Two hours after injection, the perilymph concentration was approximately 43% that of serum, and at 4 hours it was approximately 50% that of serum. Juhn et al[12] reported that perilymph concentration in the chinchilla was only 20% that of the serum level 2 and 4 hours after an intraperitoneal injection of salicylate. It is apparent from the data that there may be important species differences in salicylate uptake into perilymph, differences that may be critical in explaining discrepancies in ototoxic effects across species. Thus, the third goal of the project was to determine the relationship of serum salicylate level to perilymph salicylate level in the chinchilla.

MATERIALS AND METHODS

Drug Delivery

Adult chinchillas (*Chinchilla laniger*), aged 1 to 3 years, were used as subjects. So-

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dium salicylate (100 mg/mL; osmolality, 1080 mOsm/kg) was injected intraperitoneally. Drug administration and serum testing were performed in one group of subjects (n = 7) once weekly. Serum tests were also performed on another group of animals used to assess the effects of sodium salicylate on the auditory evoked response from the inferior colliculus[13] (N = 27). Because the later subjects required extensive evoked-response testing, only one blood test was performed in most of these subjects due to time constraints and concern for animal health. For subjects used in perilymph studies (N = 12), a single drug dose was delivered and perilymph and serum were sampled simultaneously, 4 hours after injection.

Blood and Perilymph Sampling

Blood and perilymph were drawn with the animals under anesthesia (ketamine [25 mg/kg] with acepromazine [0.5 mg/kg]). Blood was drawn from the transverse sinus, as it runs along the medial section of the auditory bulla. For a complete description of the collection technique, see the report of Boettcher et al.[15] The whole blood was centrifuged and the serum drawn off for testing. Perilymph was taken from the cochlea by using a glass pipette drawn to a fine tip. The tip was inserted through the round window membrane, and the fluid was then gently drawn into the pipette by means of a syringe assembly.

Salicylate Concentration Testing

The Trinder[16] method was used to measure serum and perilymph salicylate concentrations. The serum samples were 25 μL in volume, and the perilymph samples were 10 μL. The concentration of salicylate was determined with a spectrophotometer (Milton Roy Spectronic 6200), which was calibrated with known concentrations of salicylate.

RESULTS

Time Course of Serum Salicylate Concentrations

Figure 1 shows the mean serum salicylate concentrations for three subjects measured at five different times after an injection of 450 mg/kg of sodium salicylate. Tests were performed once per subject at each time after injection. The serum concentration increased to a high level by 2 hours after injection and peaked approximately 4 hours after injection at a mean concentration of 3.22 mmol/L (51.5 mg%). The serum concentration decreased in an approximately linear manner during the period from 4 to 16 hours after injection, with decrease to half the maximum value at 10.3 hours.

To test the variability of serum salicylate concentrations within subjects, serum measurements were repeated three times at 4 hours after injection for three subjects. The Table shows the mean, range, and SDs of these measures. The SDs of the serum concentrations were very low, less than 0.31 mmol/L (5 mg%) for each subject. Thus, serum concentrations were relatively stable at the 4-hour postinjection sampling time within subjects.

Effect of Dose

Figure 2 shows average (four subjects) serum concentrations and SEs for three salicylate doses, measured 4 hours after injection. The serum concentration increased in a fairly linear manner across the range of doses used in this study. Therefore, a linear equation was fit to the data to yield the following: $SC = -0.18 + 0.104\ D$ ($SC = -2.97 + 0.104\ D$), where SC is the serum concentration and D is the salicylate dose. The correlation between serum and dose was .881 ($r^2 = .776$; analysis of variance: F ratio = 31.08, $P < .01$).

Relationship of Animal Mass to Serum Concentrations

As mentioned above, serum tests were performed on a second group of animals used to study the effects of sodium salicylate on hearing abilities. Each subject received either 300 mg/kg (N = 12) or 450 mg/kg (N = 15) of salicylate. Although all subjects in a group were given the same dose per mass (300 or 450 mg/kg), the serum salicylate concentrations varied considerably within each group. In our experience, heavier chinchillas seemed to be more susceptible to salicylate poisoning, such that animals over approximately 625 g occasionally became ill after a dose of 450 mg/kg. The effect of animal mass on serum salicylate concentration was evaluated with an analysis of variance procedure. Animal mass had a significant effect on serum salicylate concentration (F-ratio = 6.58, $P < .05$). Animal mass did not significantly interact with drug dose to affect serum level.

Relationship of Serum and Perilymph Salicylate Concentrations

Figure 3 shows the relationship of serum salicylate concentration to perilymph salicylate concentration (N = 12). All samples were taken 4 hours after an injection of either 150 (N = 4), 300 (N = 5), or 450 (N = 3) mg/kg of sodium salicylate. The correlation coefficient between serum salicylate and perilymph salicylate concentration was .842 (analysis of variance: $df = 10$, F ratio = 24.29, $P < .001$). An equation was fit to the data to yield $P = 0.403(S) - 0.30$ ($P = 0.403[S] - 4.82$), where S is serum concentration and P is perilymph concentration.

COMMENT

Pharmacodynamics of Salicylate

As described above, the time course of hearing loss due to salicylate varies across species, and thus one goal of this project was to determine the time course of serum salicylate levels in the chinchilla. Serum salicylate level reached a peak of 3.22 mmol/L (51.5 mg%) 2 to 4 hours after an intraperitoneal dose of sodium salicylate (450 mg/kg). Clearance was approximately complete by 16 hours after injection, and the half-life elimination was approximately 10.3 hours in the present study.

The only previous data on uptake of salicylate in the chinchilla were reported by Juhn et al[12] and Woodford et al.[11] Juhn et al reported that serum levels peaked approximately 0.5 to 1 hour after an intraperitoneal injection of 300 mg/kg of aspirin. Differences in drug (aspirin vs sodium salicylate) and dose level may explain the differences in the results. Woodford et al reported an average serum level of 4.08 mmol/L (65.3 mg%) approximately 3 hours after intramuscular administration of salicylate (400 mg/kg). Woodford et al may have observed higher serum levels than those in the present study due to the different route of administration.

Mitchell et al[7] reported that a single subcutaneous injection of 545 mg/kg of sodium salicylate in the guinea pig resulted in serum levels up to 3.12 mmol/L (50 mg%) 6 hours after injection. Jastreboff et al[14] reported a peak serum salicylate level of approx-

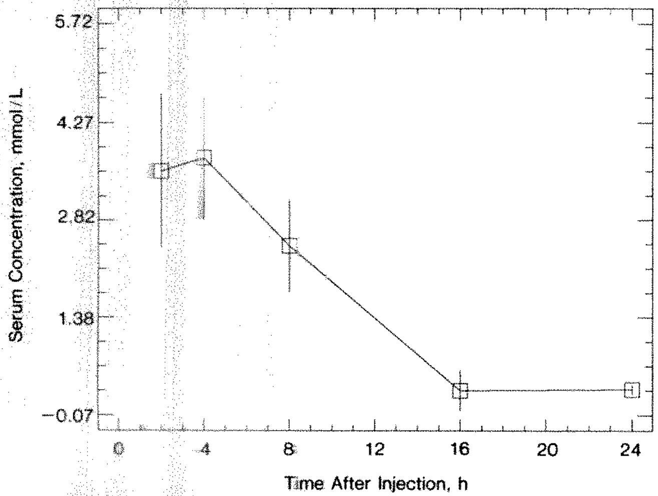

Fig 1.—Means and SDs of serum salicylate concentration at five different times after injection for three chinchillas. Sodium salicylate dose was 450 mg/kg.

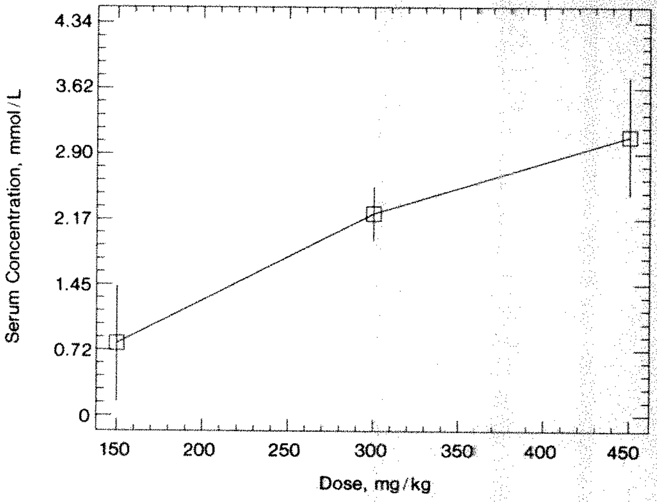

Fig 2.—Serum salicylate concentration vs dose for four chinchillas. Testing was performed 4 hours after injection.

Serum Salicylate Concentrations in Chinchillas

Test	Serum Salicylate, mmol/L (mg%)		
	Animal 1	Animal 2	Animal 3
1	2.56 (41)	3.12 (50)	2.87 (46)
2	3.00 (48)	3.31 (53)	2.50 (40)
3	2.25 (36)	3.44 (55)	2.25 (36)
Mean ± SD	2.60 ± 0.31 (41.67 ± 4.92)	3.29 ± 0.13 (52.67 ± 2.05)	2.54 ± 0.26 (40.67 ± 4.11)

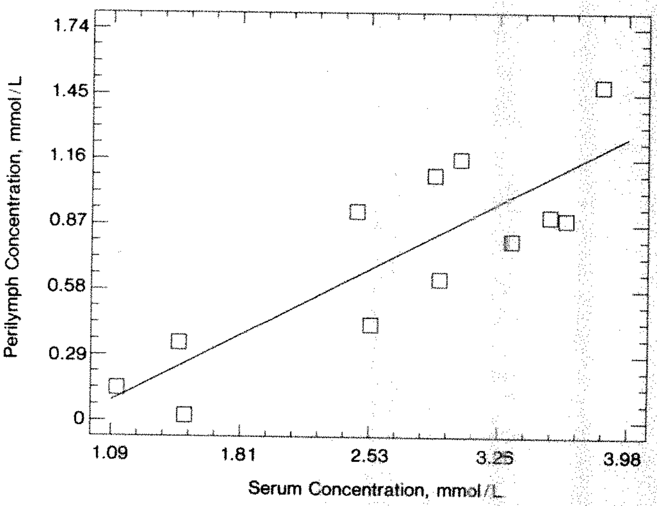

Fig 3.—Serum vs perilymph salicylate concentration for 12 chinchillas. Testing was performed 4 hours after injection.

imately 4.37 mmol/L (70 mg%) 3 to 4 hours after an intraperitoneal injection of 460 mg/kg in the guinea pig. They reported that a single intraperitoneal dose of sodium salicylate (460 mg/kg) resulted in serum levels that peaked at 3.75 to 4.38 mmol/L (60 to 70 mg%) 1.5 hours after injection in the rat. The half-life elimination could not be determined from their data. Silverstein et al[5] reported serum salicylate concentrations of 3.19 to 5.37 mmol/L (51 to 86 mg%) 6 hours after an intraperitoneal injection of sodium salicylate (350 mg/kg) in the cat. Evans et al[17] reported that blood salicylate levels for one cat were in the range of 3.62 to 4.00 mmol/L (58 to 64 mg%) 10 to 25 minutes after an intravenous injection of salicylate; levels were not less than 2.46 mmol/L 16 hours after injection. It is important to note that salicylate clears very slowly in the cat due to poor metabolism of the drug; the half-life elimination of salicylate is 38 hours in the cat.[18] Other species that have been studied include the cow (0.5 hour for half-life elimination), horse (1 hour), pig (6 hours), and dog (9 hours).[18]

In summary, serum salicylate levels peak at a similar postinjection time in the chinchilla as in the guinea pig, and only slightly later than in the rat. Furthermore, clearance in the chinchilla appears to be similar to that in the rat and guinea pig. Salicylate clearance is much faster in the chinchilla than in the cat. Interestingly, clearance is slower in the chinchilla than in the human (3 to 4.5 hours for an intravenous infusion of aspirin). It is not immediately apparent from the data why ototoxic effects differ across species. Instead, as described below, uptake of salicylate into perilymph may explain some differences in salicylate effects across species.

Variability of Serum Levels

One of the goals of the study was to determine if the within-subject variability seen in electrophysiologic correlates of salicylate ototoxic effects could be accounted for by variability in the serum levels of salicylate. The serum levels in three subjects were remarkably stable across tests, suggesting that threshold variability may not be caused by serum salicylate fluctuations.

Effect of Subject Weight

As described previously, heavy animals often achieved higher serum concentration of salicylates than did lighter animals given the same dose per mass. Analysis of variance suggested that both dose and weight significantly affected serum salicylate concentration, but that the variables did not interact. The weight of the animal presumably affected serum levels because of the higher ratio of fat to body mass in the heavier animals. Although we do not have quantitative data to support this argument, we have observed that heavier animals (>625 g) have a much higher fat content throughout the body than lighter animals. Salicylates bind to serum proteins, primarily serum albumin, and less than 5% of salicylate binds to lipids and fatty acids.[1,18] This observation suggests that to achieve similar blood concentrations across subjects, the dose should be calculated to account for body fat.

Relationship of Serum and Perilymph Levels

In the present study, the relationship of serum to perilymph salicylate level was approximately linear ($P = 0.403[S] - 0.30$) ($P = 0.403[S] - 4.82$). Jastreboff et al[14] also reported a linear relationship between serum and perilymph concentrations for the rat. A reanalysis of their data (from Fig 2 of Jastreboff et al,[14] upper right, using milligram per deciliter values of salicylate concentration) yielded an equation of $P = 0.45(S) - 0.25$. These results indicate that perilymph salicylate levels are slightly higher in the rat than in the chinchilla for a given serum salicylate concentration. Thus, one would expect the rat to have slightly greater susceptibility to ototoxic effects of salicylates than the chinchilla.

Several other investigators have described perilymph levels of salicylate. Silverstein et al[6] reported perilymph levels of 1.56 to 2.50 mmol/L (25 to 40 mg%) 5 to 7 hours after intraperitoneal injection of salicylate (350 mg/kg) in the cat; serum levels were approximately 3.69 to 5.37 mmol/L (86 mg%) in their subjects. Juhn et al[12] reported that perilymph salicylate concentration reached a peak of approximately 0.62 mmol/L (10 mg%) 2 hours after an intraperitoneal injection of aspirin (300 mg/kg) in the chinchilla. Serum salicylate level was approximately 3.44 mmol/L (55 mg%) when the perilymph concentration reached a peak in their study.[12] By comparing the ratio of perilymph salicylate to serum salicylate, it is apparent that a higher level of salicylate is achieved in the cat than in the chinchilla. This, in addition to the slow elimination of salicylate in the cat, may account for the cat's greater susceptibility to ototoxic effects of salicylate compared with other species. However, this does not imply that the cat should be the species of choice in salicylate ototoxicity investigations, because of the unusually slow metabolism of the drug in that species. Unfortunately, data are not available on uptake of salicylate into perilymph in species such as primates. It is plausible that such species, with apparently greater susceptibility to the ototoxic effects of salicylates, may have somewhat greater uptake of the drug into perilymph than the chinchilla.

The data from the present study show that salicylate is readily taken up into perilymph in the chinchilla and that the concentration of salicylate in perilymph is predictable given the serum concentration. However, the data also suggest that the chinchilla may be somewhat less susceptible to the ototoxic effects of salicylate than other species such as the cat, because of the lower ratio of perilymph to serum salicylate concentration. This is consistent with recent data from our laboratory suggesting that threshold shifts resulting from salicylate administration, averaged across subjects, are lower in the chinchilla than in other species such as the cat, monkey, and human.[13] These are important data, given current interest in salicylate ototoxic effects and the drug's putative effects on the outer hair cell.[8-10]

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Tonsillectomy in Children Under 3 Years of Age

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• A retrospective study was performed on 190 children younger than 3 years who underwent tonsillectomy either alone or in combination with other surgical procedures at the Children's National Medical Center, Washington, DC, over a 5-year period. The average age was 2 years 4 months and average weight was 12.8 kg. The most common indication for surgery was upper airway obstruction with apnea. One hundred sixty-two of 190 patients were discharged on the day following surgery. Complications were seen in 20 (10.5%) patients, 16 requiring prolongation of hospital stay and 4 requiring readmission. However, apart from one child with cerebral palsy who had multiple postoperative complications, no other child required reintubation, blood transfusion, or return to the operating room. It is concluded that age should not be a factor in determining whether or not to proceed with a tonsillectomy.

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There has been a traditional reluctance[1,2] to perform tonsillectomy on children younger than 3 years due to the smaller margin of error in children before significant blood loss and upper airway obstruction arise.

However, since the initial studies of Noonan[3] and Menashe et al,[4] there has been an increasing awareness of obstructive complications accompanying adenotonsillar hypertrophy. Being more common in younger children,[5] this had led to younger children being considered for adenotonsillectomy. The improvements in pediatric anesthesia and the use of cautery for tonsil dissection have minimized the risks of tonsillectomy and made this surgery in children a relatively routine procedure.

To ascertain the incidence of complications following tonsillectomy in children, a chart review was performed looking at children less than 3 years of age who underwent tonsillectomy at the Children's National Medical Center, Washington, DC, over the previous 5 years.

MATERIALS AND METHODS

Charts were reviewed of all children less than 3 years old who underwent tonsillectomy with or without additional surgical procedures from January 1, 1984, to December 31, 1988. The surgery was performed by attending physicians, fellows, and residents in the Department of Otolaryngology, and by visiting otolaryngologists with admission and surgical privileges at our hospital.

Operative blood loss, as estimated by the anesthesiologist, was noted. To calculate blood loss as a percentage of blood volume, blood volume was estimated at 7.5 mL per 100 g of body weight.[6] Age, sex, surgical procedure(s), indications, surgical technique, weight, duration of hospital stay, and complications were recorded.

RESULTS

A total of 2169 children underwent tonsillectomy between January 1, 1984, and December 31, 1988. One hundred ninety of the children (8.9%) were less than 3 years of age. The average age was 2 years 4 months. Ninety-one children were 30 months or older, 55 were between 24 months and 30 months, 35 were between 18 months and 24 months, and 9 were under 18 months of age, the youngest being 10 months. One hundred twenty-three were male (65%) and 67 were female (35%).

Only 13 of 190 patients underwent tonsillectomy without adenoidectomy. Five of them had undergone adenoidectomy previously; the adenoids were not found to be enlarged in 7, and 1 child had a submucus cleft palate. Seven patients had direct laryngoscopy and bronchoscopy in addition to tonsillectomy and 66 had an ear procedure that included examination of ears, myringotomy, and insertion or removal of ventilating tubes.

The indications for tonsillectomy could be ascertained in 170 cases and are listed in Table 1, the most common indication being upper airway obstruction with apnea.

Table 1.—Indications for Tonsillectomy

Indication	No.
Recurrent tonsillitis	26
Nasal obstruction with labored respiration	65
Apnea	72
Cyanotic episodes	2
Right ventricular hypertrophy/cardiomegaly	2
Acute upper airway obstruction	2
Tonsillar mass	1

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Table 2.—Complications Following Tonsillectomy

Complications	No.
Upper airway obstruction	3
Apneic episode	1
Pharyngeal edema	1
Pneumonia	2
Fever, unknown cause	2
Delay in oral feeds	5
Exacerbation of asthma	1
Secondary hemorrhage, requiring readmission	1
Dehydration requiring readmission	3

The tonsillectomy techniques were noted in 183 cases and consisted of the following: cautery dissection in 61, blunt dissection and hemostasis by cautery with or without sutures or ligatures in 111, and by blunt dissection and hemostasis by sutures or ligatures in 11.

Details of weight were available for 173 patients. The mean weight was 12.8 kg and ranged from 8.1 to 22 kg. Twenty children weighed 15 kg or more, 75 were between 12.5 and 15 kg, 66 between 10 and less than 12.5 kg, and 12 weighed less than 10 kg.

An estimation of blood loss was made in 156 patients. The mean was 50 mL. Seventy-five patients lost less than 50 mL, 61 lost between 50 and less than 100 mL, and 20 lost 100 mL or more. Maximum blood loss was 200 mL. Average blood loss, expressed as a percentage of blood volume, was 5.4%. Eighty-seven patients lost less than 5% of blood volume, 56 lost between 5% and less than 10%, and 13 lost 10% or more. Of the latter group of 13, in whom blood loss was significant, 6 patients lost less than 10.5% of blood volume and another 5 lost less than 15%. Two patients lost 19.9% and 21.2% of blood volume, respectively.

One hundred sixty-two of 190 patients were discharged on the day following surgery, 19 were discharged on day 2, 5 on day 3, and 1 each on days 4, 5, 8, and 26.

Complications necessitating either prolongation of routine hospital stay or requiring readmission were seen in 20 patients (10.5%).

One patient, a 16-month-old child with cerebral palsy and severe upper airway obstruction with cor pulmonale, had a prolonged and complicated postoperative course. This included primary and secondary hemorrhage, both of which required blood transfusion, upper airway obstruction requiring reintubation, pneumonia, hypertension, and marked delay in oral feeding.

Complications in the remaining 19 patients are listed in Table 2. Four patients (2.1%) required readmission, 1 with secondary hemorrhage and 3 with dehydration. With the exception of the child with cerebral palsy, no other patient required reintubation, blood transfusion, or return to the operating room.

COMMENT

In 1979 Helmus[7] reported a series of 109 children younger than 3 years who underwent adenotonsillectomy using the guillotine technique over a 5½-year period. All children except one were discharged by the first postoperative day. One child who also underwent excision of a branchial cyst was discharged on the second postoperative day. The apparently low rate of complications may have been due to the indication for surgery, which was recurrent tonsillitis, with none of the patients having upper airway obstruction as their main symptom. In our series all patients with postoperative airway obstruction had preoperative airway obstruction from adenotonsillar hypertrophy, with one patient also suffering from cerebral palsy.

Four children in Helmus' series,[7] however, required readmission, three with secondary hemorrhage and one with dehydration. The readmission rate was 3.7% compared with 2.1% in this series.

The mean blood loss of 50 mL in this series is comparable with the findings of Arora and Marford[8] who reported a mean blood loss of 48 mL. However, because that series included children between the ages of 3 and 12 years old, the blood loss expressed as a percentage of body weight was only 2.9% compared with 5.4% in our series. An alarming fact was the loss of 10% or more of blood volume in 13 patients, leading us to conclude that while tonsillectomy in this group of patients is acceptable, intraoperative bleeding can be a major complication if not controlled quickly and meticulously.

The one child who had a prolonged and complicated postoperative course was a 16-month-old patient with cerebral palsy. Tonsillectomy in cerebral palsy is known to be associated with significant incidence of postoperative complications and a prolonged hospital stay.

Although the complication rate following tonsillectomy was 10.5% in this series, with the exception of the child with cerebral palsy, no other child required reintubation, blood transfusion, or return to the operating room. Special attention should be paid to quickly control intraoperative bleeding. Patients undergoing surgery to relieve upper airway obstruction may develop airway complications in the immediate postoperative period and should be monitored carefully. The decision to perform tonsillectomy should be made without regard to the age of the patient, provided that surgery is carried out for appropriate indications and is performed in an appropriate institution.

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The Pathologic and Thermal Effects of Gold Vapor Laser Photodynamic Therapy on the Larynx

Experimental Study

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• A gold vapor laser, which emits short pulses of light at a wavelength of 628 nm, was used to deliver varying amounts of energy (30 to 120 J/cm²) to the presensitized (dihematoporphyrin ether) canine larynx. Between 30 and 60 J/cm², the larynx appeared normal, and when 70 to 100 J/cm² was applied, only mild edema and erythema were seen. Simultaneously, a thermocouple probe was used and a 0.4°C to 1.5°C temperature rise found. Thus, the gold vapor laser seems capable of achieving the therapeutic photosensitizing effect without causing significant laryngeal edema or thermal activity.

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Photodynamic therapy (PDT) has been used for the treatment of benign and malignant tumors in humans and animals with encouraging results.[1-4] The therapy is based on the ability of a photosensitizing agent to be absorbed and preferentially retained by rapidly growing tissues.[5]

Hematoporphyrin derivative (HPD) is a powerful photosensitive dye that, when activated by light of the appropriate wavelength, produces microvascular damage and cytotoxic agents leading to the destruction and death of tissues in which it has localized.[6] Since HPD is only minimally present in surrounding normal tissues at the time of light exposure, damage to normal tissue caused by dye activation should be minor.

The optimum wavelength for the light activation of PDT has been established at 630 nm, which adequately penetrates tissues and sufficiently activates HPD[7] and the purified form, dihematoporphyrin ether. The commonly used light source for PDT is the tunable argon pump-dye laser. This instrument produces a continuous monochromatic wave of coherent light at a wavelength of 630 nm. Although this system is an effective light source, it requires large amounts of electrical power and has a limited power output capability.

Recently, the gold vapor laser (GVL) has been introduced for use in PDT.[8,9] Although the GVL is not tunable, it is more efficient and offers greater power outputs while requiring less electrical energy than the pump-dye laser. Whereas the pump-dye laser produces continuous-wave light, the GVL emits pulsed light at a wavelength of 628 nm with high peak power.[10,11]

The emission of the GVL is characterized by short pulses of light interrupted by an off time in which no light is emitted. The laser emits a 20-nanosecond pulse of light followed by an off time of 12.5 microseconds, and then continues this on-off cycle. Each pulse has a high peak intensity (10 kW), and the amount of laser light delivered is the sum total of the individual laser pulses for the total time that the laser shutter is open.

In contrast, the light emission of the pump-dye laser is continuous for as long as the laser shutter is open. Thus, for the pump-dye laser there is no peak power or pulse energy measurement, only average power output.

Using a pump-dye laser, Shikowitz et al[5] demonstrated the efficacy of HPD in controlling cutaneous rabbit papillomatosis caused by the rabbit papillomavirus. Laryngeal papillomas are

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caused by one or more of the human papillomaviruses; however, laryngeal papillomas are superficial lesions and significantly less keratinized than their cutaneous counterparts, making them very susceptible to light penetration for PDT.[5]

Few clinical patients have received PDT for carcinoma of the larynx. Dahlman et al[12] treated one patient with 27 J/cm² delivered by an argon pump-dye laser and found a clinical response at the tumor site with minimal surrounding tissue reaction. Using a GVL, Gluckman et al[13] successfully treated a relatively superficial cancer along the left true vocal cord. Because of anxiety regarding glottic edema, a temporary tracheostomy was performed.

Abramson et al[6,14] used a tunable pump-dye laser to determine the thermal and pathological effects of PDT on the canine larynx. Before utilizing the GVL as an activating source for laryngeal PDT, a similar model system was used to establish the thermal and pathological values.

MATERIALS AND METHODS

Methods

Three hours before surgery, 3 mg/kg of dihematoporphyrin ether (Photofrin II, QLT Phototherapeutics, Inc, Vancouver, Canada) was intravenously injected into healthy mongrel dogs weighing 8 to 13 kg. Anesthesia consisted of 30 mg/kg of pentobarbital sodium. At surgery, the dogs were spontaneously breathing and placed in the supine position with the head stabilized, and a specially designed laryngoscope with multiple ports was passed through the mouth to expose the endolarynx.

With an alligator forceps, a 33-gauge copper miniature hypodermic thermocouple probe was placed through the laryngoscope and inserted immediately below the epithelium (1 to 2 mm) of the right vocal cord. The thermocouple was then connected to a thermometer (Omega Digital 450-ATT, Omega Engineering, Inc, Stamford, Conn) and serial readings were obtained to a sensitivity of 0.1°C.

A GVL (Metalaser Technologies, North Ryde, New South Wales, Australia) was used to achieve a red output for activating the photosensitive compound. The instrument delivered monochromatic light at a wavelength of 628 nm. The pulse width was 20 nanoseconds and the pulse repetition frequency was 8 to 10 kHz. The peak power was 10 kW.

A 1.5-cm cylindrical diffuser quartz fiber was attached to the laser. At this point, whenever the laser shutter was open, appropriate eye protection was worn. The light intensity was calibrated by placing the cylindrical diffuser tip into an integrating sphere. The intensity of the laser output was attenuated to 500 mW.

After fiber calibration was completed for each trial, the flexible quartz fiber was placed through the center port of the laryngoscope and into position within 5 to 15 mm of the free edge of the right vocal cord. By varying the time of light exposure, the GVL was used to deliver varied amounts of total energy ranging from 30 to 120 J/cm² at a fixed light intensity of 500 mW.

Five dogs serving as controls had serial temperature readings recorded without having been given the photosensitizing dye. Thirteen dogs were given 3 mg/kg of dihematoporphyrin ethers 3 hours before surgery, and then varying amounts of laser energy were delivered with simultaneous and serial temperature readings obtained. One dog was given 0 to 70 J/cm² of 628-nm light, with serial temperature readings obtained during the treatment and recovery phases.

At 24 hours after surgery, potassium chloride solution was administered intravenously in sufficient amounts to kill the dog. A total laryngectomy including the upper trachea was immediately performed and the interior visualized via a posterior incision.

Specimen Analysis

Observations were recorded and graded (1+ to 3+) as to the degree of edema and erythema present in the supraglottic, glottic, and subglottic regions. Gross specimen photographs were taken (using a Nikon FE2 camera, ringflash, and Kodachrome ASA 64 film) at f-8 and 35 cm from the larynx. Representative tissue samples were fixed in 3.7% formaldehyde solution, dehydrated, embedded in paraffin, sectioned at 5 μm, and routinely stained in hematoxylin-eosin-Y.

RESULTS

Vocal Cord Temperatures

During PDT with dihematoporphyrin ether, the maximum change in temperature ranged from 0.4°C when 60 J/cm² was delivered to 1.5°C for 110 J/cm² (Table 1). The control group (without dihematoporphyrin ether) showed the maximum change in temperature to range from 0.5°C when 30 J/cm² was delivered to 1.9°C for 120 J/cm² (Table 1).

When 70 J/cm² was given (Fig 1) over a period of 140 seconds, a maximum temperature change of 0.7°C was achieved. When laser light was discontinued, a rapid falloff in vocal cord temperature was noted, and at approximately 100 seconds after light exposure starting temperature was reached.

Pathological Examination

When increasing amounts of total energy were delivered to the presensitized dihematoporphyrin ether-treated canine larynx, progressive amounts of edema and erythema were observed throughout the supraglottic, glottic, and subglottic regions (Table 2, Fig 2).

There appeared to be three energy zones that resulted in different grades of tissue response. On gross examination, between 30 and 60 J/cm², the larynges appeared to be normal or with only very mild erythema noted. Minimal histological changes were observed at these energy levels and, when found, consisted of focal exocytosis of polymorphonuclear leukocytes into the epithelium, mild vascular congestion, perivascular inflammation, and edema.

When 70 to 100 J/cm² was delivered, the mild edema and erythema observed grossly was accompanied by similar but more pronounced histological changes. At 100 to 120 J/cm², mild to moderate edema and erythema were noted grossly. At these levels, the larynges showed, in addition to the microscopic changes noted above, areas of necrosis of seromucous glands.

A definite variability in individual susceptibility was observed, with a single case at 50 J/cm² showing moderate histological changes and one at 100 J/cm² showing minimal changes.

No deaths, obstructing supraglottic edema, or subglottic hemorrhage was found in any of the cases.

COMMENT

Photodynamic therapy was first performed by Jesionek and Tappeiner[15] in 1903 utilizing eosin to treat human tumors. In 1960, Lipson and Blades[1] showed that HPD is a powerful photosensitive dye that can cause destruction and death of tissues in which it has collected when activated by the

Table 1.—Temperature of Vocal Cord After Gold Vapor Laser Energy (628 nm) Exposure

Total Energy, J	Maximum Change in Temperature, °C	Baseline Temperature, °C	Temperature, °C, at Interval Energy, J/cm²											
			10	20	30	40	50	60	70	80	90	100	110	120
					Pretreated*									
30	0.5	36.1	36.4	36.5	36.6	...	...	...	...	...	...	...	...	...
40	0.8	36.5	37.7	37.0	37.2	37.3	...	...	...	...	...	...	...	...
40	0.8	36.4	36.6	36.8	37.0	37.2	...	...	...	...	...	...	...	...
40	0.9	36.2	36.6	36.8	36.9	37.1	...	...	...	...	...	...	...	...
50	0.6	35.7	35.8	36.0	36.1	36.2	36.3	...	...	...	...	...	...	...
60	0.4	37.4	37.4	37.5	37.6	37.6	37.7	37.8	...	...	...	...	...	...
70	0.7	36.2	36.5	36.6	36.6	36.7	36.8	36.8	36.9	...	...	...	...	...
80	1.1	36.2	36.6	36.8	36.9	37.0	37.1	37.2	37.2	37.3	...	...	...	...
90	0.5	36.9	37.0	37.1	37.3	37.4	37.4	37.4	37.4	37.4	37.4	...	...	...
100	0.8	37.2	37.4	37.6	37.6	37.8	37.8	37.8	37.9	37.9	37.9	38.0	...	...
110	1.0	36.0	36.2	36.5	36.8	36.9	37.0	36.9	37.0	36.8	36.9	37.0	36.9	...
110	1.5	36.2	37.1	37.4	37.7	37.5	37.3	37.2	37.2	37.2	37.2	37.2	37.2	...
120	0.7	37.4	37.6	37.8	37.9	38.1	38.1	38.1	38.0	38.0	38.0	38.0	38.0	38.1
					Control									
30	0.5	36.2	36.4	36.5	36.7	...	...	...	...	...	...	...	...	...
50	0.7	36.0	36.2	36.4	36.6	36.7	...	...	...	...	...	...	...	...
80	1.2	36.4	36.6	36.7	36.9	37.0	37.2	37.4	37.6	37.6	...	...	...	...
100	1.6	35.9	35.9	36.2	36.4	36.5	36.7	36.8	36.9	37.2	37.4	37.5	...	...
120	1.9	36.4	36.5	36.7	36.9	37.0	37.2	37.4	37.6	37.9	38.0	38.1	38.3	...

*Pretreated with dihematoporphyrin ether.

appropriate wavelength of light. Although early studies with HPD showed promise, results with this crude mixture were inconsistent. Lipson et al[16] demonstrated that HPD prepared by dissolving the crude mixture in glacial acetic acid and concentrated sulfuric acid, then adjusted to a pH of 7.4, was a better localizer in malignant tissues than was its crude precursor. By using an alkaline hydrolysis of HPD, Dougherty et al[17] modified the structure of hematoporphyrin to produce a tumor-localizing fraction identified as dihematoporphyrin ether.

The GVL consists of a ceramic tube in which pellets of the metal are placed and surrounded by high-temperature insulation. Outside the latter is a water jacket that serves to remove the excess heat from the system. As a temperature of 1300°C is achieved, the gold becomes liquid and produces a low-pressure vapor throughout the ceramic tube. Because of the physical properties of the gold atoms, the lasing is transitory, beginning at the start of the electrical pulse but ending well before the discharge has stopped. The metal atom returns to a normal state very rapidly, a characteristic that allows operation of the laser at a relatively high repetition rate.

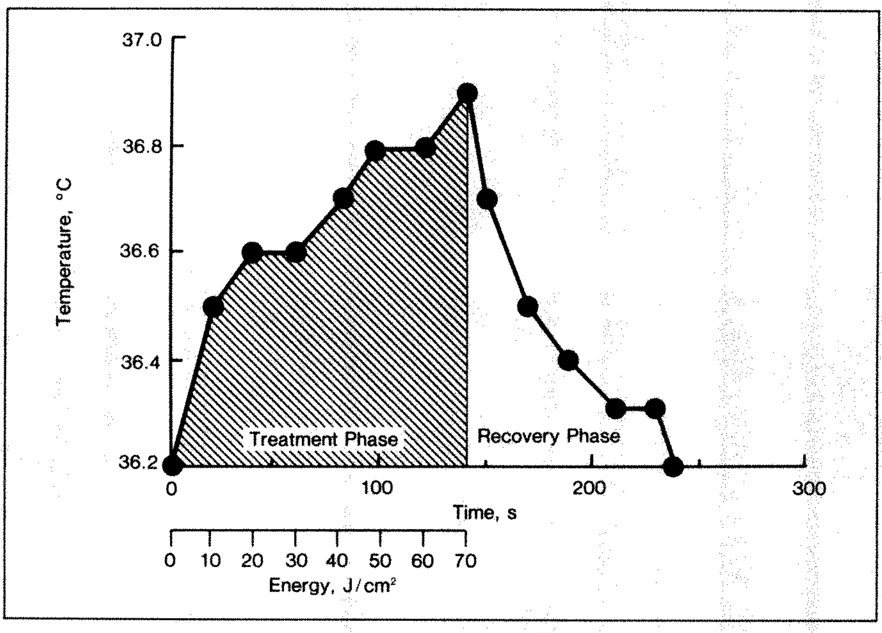


Fig 1.—Temperature of vocal cord during and after gold vapor laser exposure.

It is necessary to investigate the differences between continuous-wave and pulsed light to optimize PDT. Bellnier et al[18] found pulsed light (632 nm, 620 nm) to be ineffective in activating HPD in vivo. However, this finding may be due to the use of inappropriate pulse characteristics. The light source used produced pulses with a width of 1.6 microseconds at a frequency of 2 to 4 Hz.

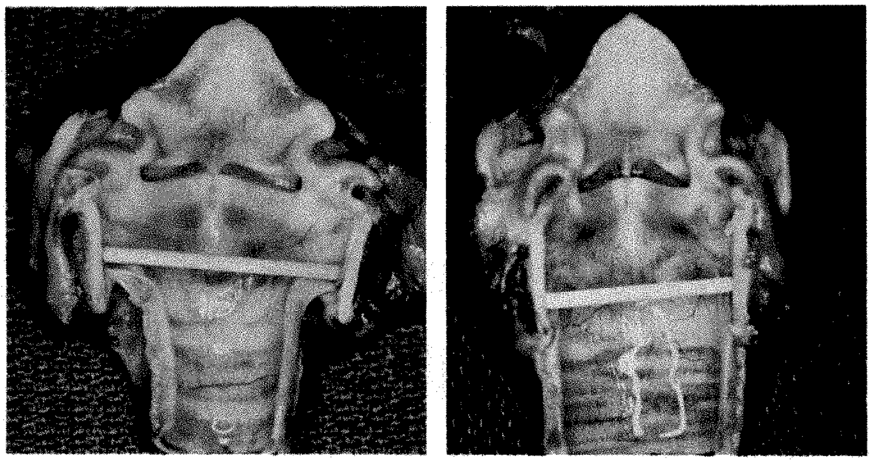
Cowled et al,[10] using a GVL (627.8 nm; pulse width, 50 nanoseconds; pulse frequency, 10 to 14 kHz), found equal effectiveness of PDT for pulsed and continuous-wave red light. Other reports[8,9,13] support this claim.

Still other investigations[11,19,20] have suggested that the high-peak-power pulses of the GVL result in deeper penetration of light than that achieved

Table 2.—Postmortem Findings* of Larynges 24 Hours After Photodynamic Therapy

Total Energy Applied, J/cm²	Edema			Erythema		
	Supraglottic	Glottic	Subglottic	Supraglottic	Glottic	Subglottic
30	0	0	0	0	0	0
40	0	0	0	0	0	0
40	1+	0	0	1+	0	0
50	0	0	0	1+	0	1+
60	0	0	0	0	0	0
70	1+	1+	0	1+	0	0
80	1+	1+	1+	1+	0	0
90	1+	2+	1+	1+	1+	1+
100	1+	1+	1+	1+	1+	1+
110	2+	1+	1+	1+	1+	1+
110	2+	1+	1+	1+	1+	1+
120	2+	2+	1+	1+	2+	2+

*Maximum response, graded 1+ to 3+.



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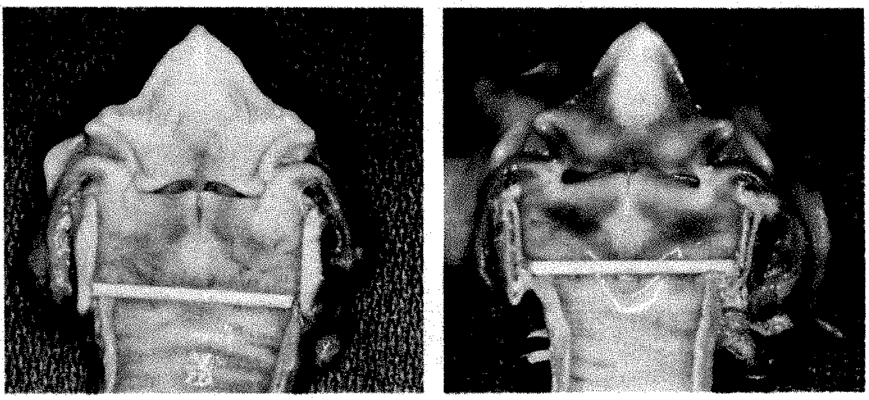

70 JOULES 120 JOULES

Fig 2.—Progressive degrees of tissue response that occur when 30 to 120 J/cm² is delivered to canine larynx.

by the pump-dye laser set at similar wavelength and power output. The pulsed light of the GVL is believed to increase the excitation of HPD throughout a larger volume of tissue.

However, LaPlant et al,[21] using a GVL (628 nm; pulse width, 40 nanoseconds; pulse repetition frequency, 5 kHz) found no significant difference in the transmission of pulsed and continuous-wave light through rabbit muscle. They concluded that the GVL does not penetrate deeper into tissue than continuous-wave light of a similar wavelength delivered at the same average power level.

It is clear that the differences between continuous-wave and pulsed light for dye activation in PDT require further investigation. In addition, it would be interesting to investigate the effects of varying pulse length or peak power magnitude on dihematoporphyrin ether activation and thermal rise.

Abramson et al[6] investigated the pathological effects of PDT on the canine larynx using an argon pump-dye laser. They observed the effects of PDT on the supraglottic, glottic, and subglottic regions of the larynx and noted four apparent energy zones that resulted in different grades of tissue response. Between 10 and 40 J/cm², the larynx appeared normal except for minimal subglottic erythema. When 50 to 70 J/cm² was delivered, mild edema and erythema were observed. At 80 to 100 J/cm², mild to moderate edema and erythema were noted. Above 100 J/cm², moderate to severe edema and erythema were seen, with two upper airway deaths observed.

In this experiment using a GVL, there was only a mild to moderate degree of edema and erythema, which developed after 70 to 100 J/cm² was delivered. No deaths occurred, and no obstructing supraglottic edema or subglottic hemorrhage was found in any of the larynges.

Using the pump dye laser, Abramson et al[14] studied the thermal effects of PDT on the canine larynx. A rise in vocal cord temperature of 0.5°C to 2.1°C was achieved after varying the total energy delivered from 10 to 150 J/cm², respectively, at a constant intensity of 500 mW. The magnitude of temperature increase was proportional to the total energy delivered and was similar for both the dihematoporphyrin ether-treated group and the control (untreated) group. After the laser light stimulus was discontinued, a rapid falloff in the thermal energy within the vocal cord was found.

Though limited studies have been performed to investigate the efficacy of the GVL for PDT, no thermal studies have been reported. Whether cell death and tumor destruction are a result of singlet oxygen formation alone[22] or a combination of tumoricidal effects such as mild hyperthermia,[23] singlet oxygen production, and/or reduced vasculature is not resolved.

Moderate hyperthermia within the range of 41°C to 43°C, has been shown to destroy malignant cells selectively without damage to normal cells when various experimental tumors were heated.[24,25] However, when cells were heated above 43°C, selectivity was lost and normal cells were destroyed as well. If enough power is delivered during PDT irradiation, considerable heat can be generated.[14]

In theory, the thermal effects of the GVL should be less than those of the pump-dye laser at equal average delivered power. Although the GVL produces high-peak-power pulses, the relatively long delay between pulses is believed to allow adequate tissue cooling, thereby reducing the overall heating effects of the laser light.

In this experiment using the GVL, the maximum temperature change of PDT on the canine larynx was 0.6°C less than the argon pump-dye laser. This supports the claim that the pulsed delivery of light allows for added tissue cooling.

The air-containing larynx, especially when undergoing spontaneous respiration or jet ventilation, acts as an excellent dissipater of thermal energy. Furthermore, the ability of laser light to heat tissue is thought to depend on power intensity, which was relatively low in both studies investigating the thermal effects of the GVL and pump-dye laser.

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The Expression of α Vascular Smooth-Muscle Actin in Salivary Gland Tumors

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• In an attempt to determine if both pleomorphic adenomas and adenoid cystic carcinomas are derived from myoepithelial cells, 23 pleomorphic adenomas, 22 adenoid cystic carcinomas, and 17 normal salivary glands were examined immunohistochemically by using monoclonal antibodies directed against actin (HUC1-1, 1A4), keratin (AE-1, 34β E12), and vimentin (V9). In normal salivary glands, the myoepithelial cells demonstrated a positive reaction to the monoclonal antibodies against actin and only rarely reacted with those against vimentin. No reaction to those against keratin was noted. In pleomorphic adenomas, cells that histologically resembled myoepithelial cells displayed a positive reaction to HUC1-1 in 60.9% and to 1A4 in 65.2%. In adenoid cystic carcinoma, 59.1% of cases demonstrated a positive reaction to both HUC1-1 and 1A4. These results supported the hypothesis that the majority of pleomorphic adenomas and adenoid cystic carcinomas arise from cells of myoepithelial origin.

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Pleomorphic adenoma and adenoid cystic carcinoma are unique tumors with both ectodermal and mesenchymal histologic features. In an effort to understand these features and the histogenesis of the tumors, many studies have been performed by using light microscopy,[1-3] electron microscopy,[1-4] and immunohistochemistry.[3,5-8] The results of these studies suggested that the myoepithelial cells constitute the bulk of the tumor tissue[6] and play an important role in their histogenesis. Other studies, however, suggested that the tumor originates from the epithelial cells of the ductal-acinar unit,[1,2,4] especially the intercalated duct,[5] or myoepithelial/basal cell system,[9] or that these neoplasms are true mixed tumors consisting of both epithelial and mesenchymal cells.[10,11]

Immunohistochemical studies of salivary glands and their tumors have demonstrated a wide variety of antigens present, many of which have been used as markers of myoepithelial cell differentiation (S100 protein, keratin, vimentin, actin, and myosin[5,6]). These, however, are not specific for myoepithelial cells, and are often expressed by acinar cells and ductal epithelium. The relationship between the myoepithelial cell and salivary gland tumors thus remains inconclusive.

Recently, subtype- and isoform-specific monoclonal antibodies to actin have become available.[12-15] Two such antibodies that do not recognize the β and α cytoplasmic actins but react with muscle actin isoforms, 4.2-kd protein, were used in this study to examine specifically the myoepithelial component of salivary gland tumors. One antibody (HUC1-1) recognizes all four mammalian muscle actin isoforms (α cardiac, α skeletal, α vascular, and α enteric), while the other, 1A4, recognizes only the vascular smooth-muscle isoform. The localization of muscle actin in myoepithelial cells in normal salivary glands and the tumor cells of pleomorphic adenoma and adenoid cystic carcinomas is compared with the results obtained by using monoclonal antibodies to keratin (AE-1, 34β E12) and vimentin (V9).

MATERIALS AND METHODS

Materials

Tissue from 23 pleomorphic adenomas and 22 adenoid cystic carcinomas were retrospectively reviewed at the University of Cincinnati (Ohio) Medical Center. In addition, 17 normal salivary glands, obtained from surgical specimens that included major salivary glands as part of the dissection, were evaluated. All tissues had been fixed in 3.7% buffered formaldehyde solution, embedded in paraffin, and processed routinely.

Immunohistochemical Technique

Following deparaffinization, sections to be stained with HUC1-1 (J. L. Lessard [monoclonal antibody developer], Children's Hospital Research Foundation, Cincinnati, Ohio), AE-1 (Hybritech, Inc, San Diego, Calif), and 34β E12 (ENZO Diagnostic, Inc, New York, NY), were treated with 0.1% trypsin and 0.1% calcium chloride (pH, 7.7) for 30 minutes at 37°C. After washing well with phosphate-buffered saline solution (PBSS), 0.15-mol/L sodium chloride in 0.01-mol/L phosphate buffer (pH, 7.2 [PBSS]), all sections were incubated in 5% nonfat dry milk that contained 0.5% nonidet P-40 and in 0.01% sodium aside for 30 minutes at room temperature to

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block nonspecific binding. After washing with PBSS, the sections were reacted with the primary antibody at the following dilutions for 30 minutes in a moist chamber: HUC1-1, 1:400; 1A4 (Sigma Chemical Co, St Louis, Mo), 1:5000; AE-1, 1:200; 34β E12, and vimentin V9 (Sigma Chemical Co), 1:150. The tissues were then rinsed three times with PBSS, the sections were reacted with biotin-labeled horse anti-mouse IgG (Vector Laboratories, Burlingame, Calif) for 30 minutes. After washing three times with PBSS, the endogenous peroxidase activity was blocked by a 15-minute incubation in methanol that contained 0.3% hydrogen peroxide. The slides were rinsed with PBSS, and the tissue was overlaid with a peroxidase-avidin conjugate for 30 minutes. Following washing in PBSS, the sections were immersed in a diaminobenzidine-hyper oxide reagent (0.02% 3,3-diaminobenzidine tetrahydrochloride; 0.005% H_2O_2; 0.05 mol/L TRIS buffer; and pH, 7.6) for 10 minutes, counterstained with Harris' hematoxylin, dehydrated in ethanol, cleared in xylene, and coverslipped by using permount.

Immunohistochemical staining for each antigen was independently assessed on a scale of none, focal and/or weakly positive, or strongly positive, as judged from the staining intensity in the tumor cells.

In addition to using five different monoclonal primary antibodies, a negative control without the application of a primary antibody was employed, uniformly demonstrating no reaction.

RESULTS

Light Microscopy Findings

The pleomorphic adenomas consisted of ductal, myoepithelial, squamous epithelial, cartilage, solidly proliferative, and spindle cells in myxomatous stroma.

The adenoid cystic carcinomas demonstrated the following four histologic patterns, in variable proportions: basaloid, cribriform, trabecular, and reticular. The basaloid pattern demonstrated solid sheets of relatively small cuboidal cells and consisted of individual units filled with these tumor cells. The cribriform pattern was characterized by nests of tumor cells with a "Swiss cheese" configuration, containing pseudocyst, duct, and tumor cell islands. The trabecular pattern consisted of elongated tubular structures with a central lumen. The reticular pattern consisted of a mesh of relatively uniform polygonal cells within a dense, sclerosed stroma.

Table 1.—Immunohistochemical Findings in Normal Salivary Gland, Pleomorphic Adenoma, and Adenoid Cystic Carcinoma*

	Actin		Keratin		Vimentin, V9
	HUC1-1	1A4	AE-1	34β E12	
Normal salivary gland					
Epithelium					
Duct	–	–	+	++†	–
Acini	–	–	–	–	–
Myoepithelial cell	+	+	–	–	±
Blood vessel					
Endothelium	–	–	–	–	+
Smooth muscle	+	+	–	–	+
Pleomorphic adenoma					
Myoepithelial-type cell	+	+	±	±	±
Duct-lining cell	–	–	++	++	–
Squamous epithelium-type cell	–	–	++	++	–
Solidly proliferative cell	–	–	+	+	+
Cartilage-type cell	–	–	–	±	±
Myxoma-type cell	±	±	±	±	+
Adenoid cystic carcinoma					
Basaloid pattern	–	–	±	±	±
Cribriform pattern	+	+	±	±	±
Pseudocyst					
Duct-lining cell	±	±	+	+	±
Island	±	±	+	±	±
Trabecular pattern					
Duct-lining cell	±	±	+	+	±
Layers against stroma	+	+	±	–	±
Reticular pattern	±	±	±	–	±

*Staining was scored as no (–), moderate (+); slight (±); and intensive (++).

†Basal cells of ductal epithelium showed a positive reaction.

Immunohistochemical Findings

The immunohistochemical findings for cell types present in normal salivary glands, pleomorphic adenomas, and adenoid cystic carcinomas are summarized in Table 1, and the reaction of each antibody is presented in Table 2.

Table 2.—Positive Reaction of Each Antigen in Pleomorphic Adenoma and Adenoid Cystic Carcinoma

	%	
	Pleomorphic Adenoma	Adenoid Cystic Carcinoma
Actin		
HUC1-1	60.9	59.1
1A4	65.2	59.1
Keratin		
AE-1	100	100
34β E12	87.0	90.9
Vimentin V9	87.0	68.2

Normal Salivary Glands

Antiactin monoclonal antibodies (HUC1-1, 1A4) detected actin in the slender or triangular cells at the periphery of acini and ducts (Fig 1), corresponding to the position of myoepithelial cells. In addition, actin was observed in the cytoplasm of smooth-muscle cells of blood vessels. These two monoclonal antibodies did not show any reactivity with the ductal epithelium or the acinar epithelial cells.

The monoclonal antibody AE-1 detected keratin in all levels of the ductal epithelium (Fig 2), while 34β E12 reacted positively only in basally located triangular cells of ductal epithelium (Fig 3). However, keratin was not detected in myoepithelial cells and acinar cells by either of these two monoclonal antibodies.

The monoclonal antibody V9 occasionally demonstrated vimentin in myoepithelial cells, but not in the epithelium of the acinar, intercalated, and interlobular ducts.

Pleomorphic Adenoma

In the pleomorphic adenoma, the immunoreactivity for the two antiac-

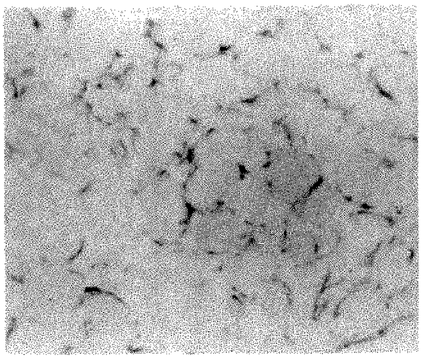

Fig 1.—Actin recognized by 1A4 was present in myoepithelial cells at the periphery of acini and ducts. Normal salivary gland tissue (avidin-biotin complex, ×200).

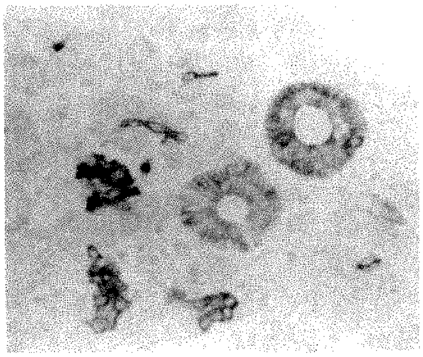

Fig 2.—Keratin detected by AE-1 localized in duct epithelium. Normal salivary gland tissue (avidin-biotin complex, ×200).

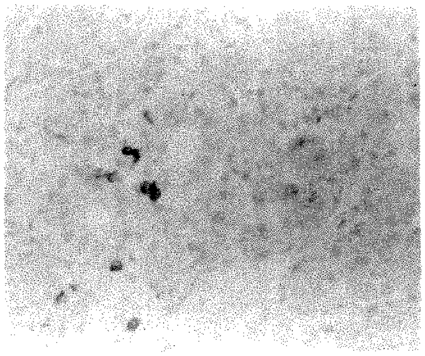

Fig 3.—Keratin recognized by 34β E12 was observed basally located triangular cells of duct epithelium. Normal salivary gland tissue (avidin-biotin complex, ×200).

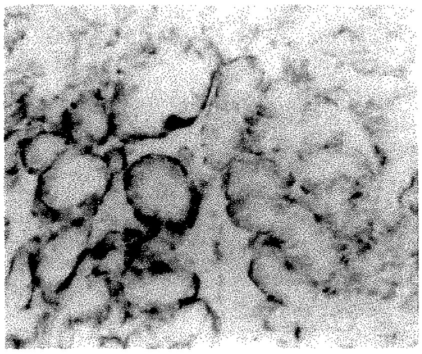

Fig 4.—Outer-layer cells surrounding duct-lining cells showed positive reaction with HUC1-1, a monoclonal antibody to actin. Pleomorphic adenoma tissue (avidin-biotin complex, ×200).

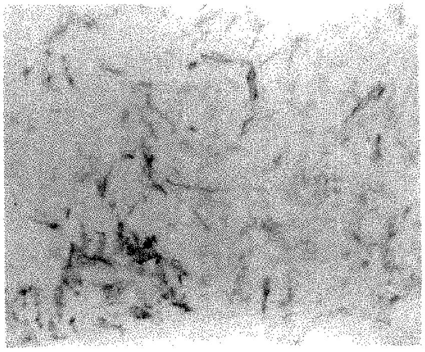

Fig 5.—Spindle cells and polygonal cells in myxomatous matrix showed positivity with monoclonal antibody 1A4 to actin. Pleomorphic adenoma tissue (avidin-biotin complex, ×200).

tin monoclonal antibodies (HUC1-1, 1A4) were similar, and no significant differences between them were recognized. Actin was noted in outer-layer, myoepithelial-type cells that surrounded inner duct-lining cells (Fig 4) and occasionally in spindle or polygonal cells in myxomatous matrix (Fig 5). Sixty percent of pleomorphic adenomas had a positive response to HUC1-1, with 13% showing moderate staining and 47.8% showing only slight staining. The monoclonal antibody 1A4 stained 65.2% of the pleomorphic adenomas; 17.4% were stained moderately; and 47.8% were stained slightly. In three cases, the tumor stained positive for just one of the two antiactin monoclonal antibodies. These three cases showed focal immunoreactivity. Those that were negative for actin demonstrated a predominantly myxoma-type histology under the light microscope.

The monoclonal antibody AE-1 detected keratin in squamous epithelial cells, duct-lining cells, spindle cells in myxomatous stroma, solidly proliferative areas, and occasionally in myoepithelial-type cells. However, keratin was not found in cartilage-type cells. The monoclonal antibody 34β E12 reacted intensely in glandular epithelium, squamous epithelium, and solidly proliferative areas. In addition, myoepithelial and spindle cells in myxomatous stroma, and occasionally, cartilage revealed a positive reaction to 34β E12. All of the pleomorphic adenomas had a positive reaction to AE-1, with 91.3% showing moderate staining and 8.7% showing slight staining. The monoclonal antibody 34β E12 stained 87.0% of the pleomorphic adenomas; 69.6% were stained moderately; and 17.4% were stained slightly. In those cases that reacted negatively to 34β E12, spindle cells in myxomatous stroma was the predominant histologic finding.

Vimentin was detected by V9 in myoepithelial-type cells, spindle cells in myxomatous stroma, cartilage-type cells, and solidly proliferative areas, but could not be detected in duct-lining cells and squamous epithelium-type cells. Eighty-seven percent of pleomorphic adenomas stained with V9; 47.8% were stained moderately; and 39.1% were stained slightly. In those cases with a negative reaction, the light microscopy revealed predominantly spindle cells in myxomatous stroma.

Adenoid Cystic Carcinoma

No significant difference was observed by using the monoclonal antibodies to actin. In half of the tumors with a cribriform pattern, cells that formed pseudocysts reacted positively (Fig 6). Occasionally, cuboidal cells that lined ducts and solid sheets of tumor cells also were positive. In the trabecular pattern, the layers against the stroma were frequently positive, as were some duct-lining cells and solid tumor cells (Fig 7). A reticular pattern usually exhibited only a focal positive reaction, while the basaloid pattern was always negative. Adenoid cystic carcinoma stained with HUC1-1 in 59.1% of cases; 18.1% were stained moderately; and 40.9% were stained slightly. The monoclonal antibody 1A4 also stained 59.1% of these tumors;

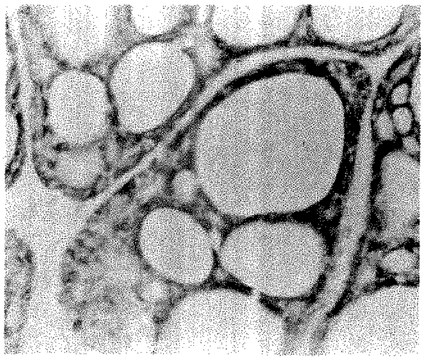

Fig 6.—Actin recognized by HUC1-1 localized in cells consisting of the pseudocysts and occasionally duct-lining cells in the cribriform pattern. Adenoid cystic carcinoma tissue (avidin-biotin complex, ×200).

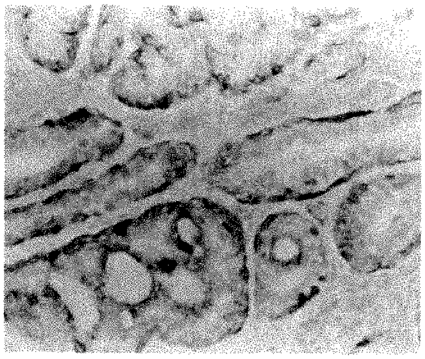

Fig 7.—Actin detected by 1A4 was present in cell layers against stroma and occasionally duct-lining cells in the trabecular pattern. Adenoid cystic carcinoma (avidin-biotin complex, ×200).

22.7% were stained moderately; and 36.4% were stained slightly. Two tumors reacted focally to only one of the two antiactin monoclonal antibodies. All basaloid pattern cases were negative as were those of a cribriform or trabecular pattern.

With AE-1, keratin was detected in duct-lining cells in the cribriform and trabecular patterns. In addition, keratin was occasionally detected in cells comprised of pseudocysts, layers against the stroma of the trabecular pattern, and the reticular pattern. By using 34β E12, keratin was demonstrated in duct-lining cells of cribriform and trabecular patterns, and also occasionally in pseudocyst cells and cellular islands of a cribriform pattern. However, layers against stroma of trabecular and reticular patterns exhibited no immunoreactivity to 34β E12. All adenoid cystic carcinomas stained with AE-1; 77.3% were stained moderately; and 22.7% were stained slightly. The monoclonal antibody 34β E12 stained 90.9% of these tumors; 54.5% were stained moderately; and 36.4% were stained slightly. The cases that did not stain with 34β E12 revealed basaloid and trabecular patterns.

Vimentin was detected in every histologic pattern, but the immunoreaction was either weak or focal. The total positive incidence was 58.2% (positive, 18.2; positive or negative, 50%). A negative reaction was noted in a portion in all histologic patterns.

COMMENT

Pleomorphic adenoma and adenoid cystic carcinoma histology has been studied by light microscopy,[1-3] electron microscopy,[1-4] and, more recently, immunohistochemistry.[5-9,11,16] Despite these numerous reports, the exact role of the myoepithelium in the histogenesis of these tumors remains controversial. Light microscopy and electron microscopy are useful only in their ability to differentiate morphologic changes. With immunohistochemical techniques, more information about the character of tumor cells, ie, the expression of intermediate filaments and other molecular markers is available. S100 protein, keratin, vimentin, actin, and myosin have been used as markers for myoepithelial cell differentiation,[5-9,16,17] with S100 protein being the most popular. It is found in normal myoepithelial cells and tumor cells of pleomorphic adenoma and adenoid cystic carcinoma. However, its presence in ductal epithelium has not been confirmed, and moreover, S100 protein is widely distributed in the nervous systems and nonneural tissues.[17] Therefore, it cannot be a specific marker for myoepithelial cells.

Actin is a ubiquitous cytoskeletal protein component of microfilaments, existing in large amounts in muscle, as well as in nonmuscle cells. Different cell types contain biochemically distinct actins. There are at least six different isoforms, distinguished by varied amino acid sequences at the amino-terminal peptide.[12-15,18,19] The localization of actin in normal myoepithelial cells and salivary gland tumors has been reported.[5,7,8,20] Because polyclonal or monoclonal antibodies that recognized the cytoplasmic actin isoforms were used, these studies have not examined antibodies specific for myoepithelial cells.[9] Therefore, we used subtype- and isoform-specific monoclonal antibodies to actin. The monoclonal antibody HUC1-1 recognizes all four mammalian muscle isoforms (*α* cardiac, *α* skeletal, *α* vascular, and *α* enteric), while 1A4 recognizes only an *α* vascular smooth-muscle actin isoform.[21] Normal myoepithelial cells and smooth-muscle cells in normal salivary gland tissues are immunoreactive with both these monoclonal antibodies, while no reaction was observed in the ductal epithelium, either its basal or acinar cells. Our results suggest that the monoclonal antibody to muscle actin is a better marker for myoepithelial cells than either keratin or vimentin. In pleomorphic adenoma, the tumor cells, showing myoepithelial differentiation morphologically, expressed an *α* vascular actin as did adenoid cystic carcinoma, except in its basaloid pattern. This basaloid pattern is composed of immature cells, and the negative reaction could be caused by the amount of actin antigens, or specifically of monoclonal antibodies. Muscle actin(s) was demonstrable in approximately 60% of all tumors examined.

In previous reports of keratin immunostaining, ductal components in various levels always expressed keratin.[5-9,16,22] Our results agree with these observations, and AE-1 and 34β E12 showed a positive reaction in all normal ductal epithelium. These monoclonal antibodies, however, showed no reaction with normal myoepithelial cells. In contrast to reports describing the expression of 50- and 58-kd keratin in normal myoepithelial cells,[8,10,22,23] we did not identify a positive reaction with 34β E12 that recognizes 56, 56.6-, and 58-kd keratin. This discrepancy may be due to the difference in the specificity of the monoclonal antibodies employed or the effect of fixation. In the tumors, keratin detected with these two monoclonal antibodies was broadly distributed throughout the tumors, particularly in squamous epithelium-type cells and duct-lining cells in both types of tumors. The monoclonal antibody AE-1 was noted to react in all of the tumors examined. Keratin detected by AE-1 was demonstrated more extensively in the tumors than keratin that reacted with 34β E12. Our results are consistent with those of previous reports that demonstrated the reliability of keratin as a marker of epithelial differentiation in most normal and neoplastic tissues.[6,17] The use of narrow-spectrum antikeratin monoclonal antibodies, which specifically detect a few members or a single member of a keratin family, may be useful for the definition of subtypes of normal epithelia.[22,23] However, tumor cells tend to alter the immunohistochemical phenotyping of keratin from original epithelium following neoplastic transformation, and the keratin subtype expressed does not appear to correlate with the histogenesis of a tumor.[23] The 50- and 58-kd pair of keratin was present not only in normal myoepithelial cells, but also in almost all keratinocytes and tumors of ectodermal origin.[23] Thus, keratin is unlikely to be a good marker for myoepithelial differentiation.

In normal salivary glands, vimentin has been reported immunohistochemically to localize in myoepithelial cells, but in general, the reactivity is focal or weak.[5,7,8,16] Our results confirmed these observations. This may be due to the specificity of monoclonal antibodies or the amount of antigen present. Vimentin staining was high in both tumors (pleomorphic adenoma, 87.0%; adenoid cystic carcinoma, 68.2%). Vimentin, however, localizes in cells of not only mesenchymal origin, but also in other germ cells and, therefore, is not a unique marker for myoepithelial differentiation and is not useful in determining tumor origin.

According to the distribution of these antigens, the presence of a muscle actin(s), with or without vimentin and keratin, provides strong evidence of myoepithelial differentiation in these tumors. In pleomorphic adenoma, cells that show mesenchymal features, and are undifferentiated, morphologically stained for a muscle actin, keratins, and vimentin. In adenoid cystic carcinoma, almost all tumor cells show these three antigens in their cytoplasm, except for immature cells that compose the basaloid pattern. The tumor cells, which were negative for muscle actin, usually revealed a positive reaction to keratin and/or vimentin. As the simultaneous localization of keratin and vimentin in tumor cells was reported in previous studies by using double-staining methods, it is unlikely that these tumors could be of a dual origin. Moreover, the negative incidence to both muscle actin and vimentin was as low as 8.7% in pleomorphic adenoma and 9.1% in adenoid cystic carcinoma. From these results, we conclude that muscle actin is a good marker for myoepithelial differentiation in normal salivary glands and salivary gland tumors. Our data support the hypothesis that pleomorphic adenoma and adenoid cystic carcinoma could arise from cells of myoepithelial origin.

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Uncontrollable Epistaxis

Angiographic Localization and Embolization

Jurgen Strutz, MD; Martin Schumacher, MD

• **The method of choice for uncontrollable epistaxis that is refractory to anterior and posterior nasal packing is controversial. In a retrospective study, the therapeutic results in 42 patients with uncontrollable epistaxis were reviewed, with special consideration of 11 cases in which the patients received angiography and embolization of branches of the internal maxillary artery. Out of this collective, only one patient received surgery, ie, transantral internal maxillary artery ligation. The results of primary embolization demonstrated the effectiveness and illustrated the potential role of embolizing procedures in uncontrollable epistaxis.**

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Epistaxis is a common occurrence. Small et al[1] reported that 60% of the adult population had experienced an episode of epistaxis and that only 6% of that population required medical treatment. Most cases of epistaxis arise from the easily accessible anterior septal area. Posterior- and superior-based bleedings, however, continue to be a problem. This is reflected in the numerous treatment regimens found in the current literature. The ascending scale of treatment starts with anterior nasal packing, endoscopic-guided electrocoagulation, and posterior nasal packing up to transantral internal maxillary artery ligation in combination with ligation of both ethmoidal arteries or ligation of the external carotid artery.

Although Sokoloff et al[2] had already mentioned the advantages of selective embolization in severe epistaxis in 1974, this method has not been widely adopted in concepts for treatment. Embolization may become a primary treatment modality in patients whose epistaxis is intractable and/or secondary to vascular abnormalities, bleeding disorders, trauma, or tumor and in medically compromised patients who are unable to undergo surgical treatment because of high anesthetic risk.

To our knowledge, only case reports have been published to date; therefore, our purpose was to study embolization as therapy in uncontrollable epistaxis. Retrospectively, all patients with uncontrollable epistaxis requiring hospitalization between 1985 and 1988 were evaluated.

PATIENTS AND METHODS

The records of all patients admitted for severe epistaxis between 1985 and 1988 were retrospectively reviewed. Our therapeutic protocol for epistaxis escalates step-by-step from anterior nasal packing to endoscopic-guided electrocoagulation and posterior nasal packing. When postnasal packing was necessary, we defined this severity as uncontrollable epistaxis. A total of 42 patients met this condition. These patients were analyzed for age, cause of epistaxis, and the method of treatment.

In 11 cases in which bleeding continued or recurred after removal of the choanal pack, angiography and embolization were performed. Before angiography was performed, a postnasal pack was again placed to tide over the critical time between onset of bleeding and definite occlusion of the bleeding source. With the patient under local anesthesia, using the femoral route, a 4F vertebral catheter or an additional tracker catheter was used for embolization. The catheter tip was advanced into branches of the external carotid artery. After selective angiography of the internal maxillary artery, embolization was carried out employing polyvinyl alcohol particles (150 to 590 μm) if there was no evidence of reflux around the catheter and if dangerous anastomoses to the internal carotid or vertebral artery could be excluded. Following each injection of polyvinyl alcohol particles, repeated angiography demonstrated the degree of distal runoff. When the flow toward the vascular lesion was abolished, there was no longer any arterial flow directing the embolic material to the periphery, and the procedure was terminated. The day after embolization, all packing was removed. In the very first part of this study, angiography and embolization were not systematically used. Transantral internal maxillary artery ligation in combination with coagulation of the ethmoidal arteries was performed as proposed by Chandler and Serrius.[3] Three patients received arterial ligature on one side.

RESULTS

The ages of the patients ranged from 23 to 76 years, with an average of 48 years. There was a 5:3 male-female ratio. Of the 42 patients studied, 28 were treated only medically; ie, after removal of the choanal pack no nosebleed recurred.

Three patients were treated surgically. Two of them were hypertensive; one was posttraumatic. All three patients were treated with unilateral transantral internal maxillary artery ligation, with additional anterior and

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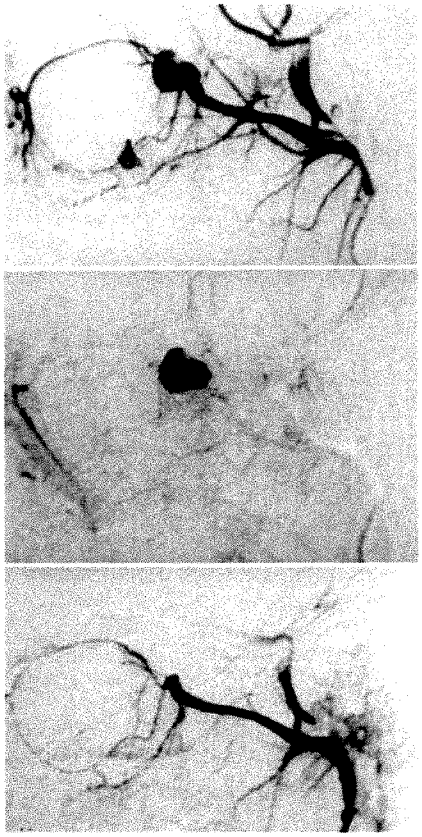
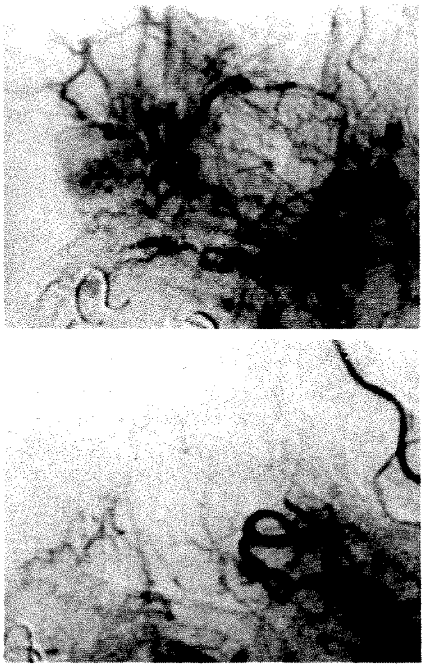


Fig 1.—Large traumatic aneurysm at the beginning of the infraorbital artery before (top) and after embolization with polyvinyl alcohol particles (bottom).

Fig 2.—Increased vascularity in the terminal area of the infraorbital artery and transverse facial branches of the internal maxillary artery before (top) and after embolization with polyvinyl alcohol particles (bottom).



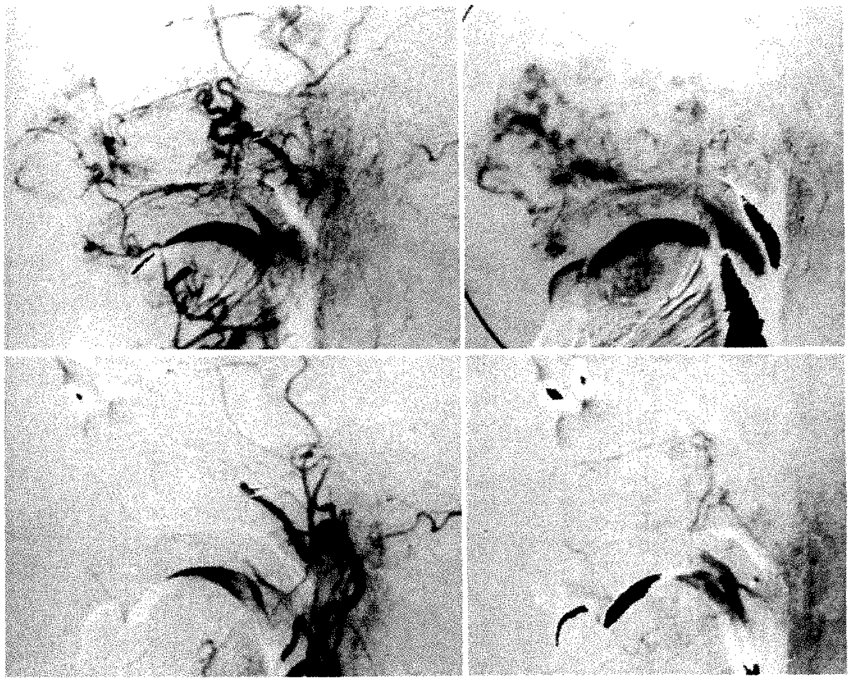


Fig 3.—Multiple vascular deformities with knots in the territory of the lingual, internal maxillary, facial, and superficial temporary arteries before embolization (top). Extensive embolization with proximal occlusion of all feeders was performed (bottom).

posterior ethmoidal coagulations in one case. In this surgical group there were no episodes of rebleeding.

The angiography and embolization group consisted of 11 patients with a 5:6 male-female ratio. Four patients were hypertensive; other causal factors were direct trauma (two patients), nasal or sinus surgery (two patients) or Rendu-Osler disease (one patient), while in two patients no causal factor was discernible. In all cases (except one) the embolizations were carried out unilaterally. Except for the patient with bilateral embolization, the clinically predicted side of the bleeding correlated well with the angiographic verification of vessel abnormalities. The actual bleeding site could be defined in most cases (Fig 1). Otherwise, an increased vascularity of the nasopharyngeal mucosa was indicated (Fig 2). In the patient with Rendu-Osler disease, angiograms demonstrated multiple vascular malformations with telangiectatic vessels in the nasal and paranasal regions (Fig 3). In each case, parts of peripheral branches of the internal maxillary artery were embolized depending on the bleeding site, ie, the infraorbital, sphenopalatine, pharyngeal, posterior nasal, posterior and superior alveolar, and descending palatine arteries. In all cases except one, the bleeding was stopped successfully. In the unsuccessful case, the internal maxillary arteries were embolized on both sides. This failure may have been the result of insufficient embolic material. The patient was treated surgically by ligation of the internal maxillary artery of one side without rebleeding. Another patient required a second embolization because of rebleeding; however, this patient has not bled since this procedure was performed.

Other than minor side effects such as muscle pain, trismus, and slight fever, there were no complications.

COMMENT

Uncontrollable epistaxis may be a life-threatening event, whether idiopathic or caused by surgical complications, hypertension, trauma, vascular malformations, tumors, or hemostatic disorders. Although with conservative therapy the failure rate varies from 26% to 52%, with a complication incidence of 2% to 50%,[4] the ascending scale of treatment should start with anterior nasal packing, endoscopic-guided electrocoagulation, and posterior nasal packing.[5-8] This method correlated well with successful medical therapy in 28 (66%) of our 42 patients.

The method of choice for control of epistaxis that is refractory to nasal packing is controversial.[9] The incidence of failure of internal maxillary ligation ranges from 10% to 15%, depending on nonidentification of the vessels, partially closed clips, and bleeding from the ethmoidal arteries. In addition, in about 6% of cases, the size of the antrum is so small because of poor pneumatization that transantral approach to expose the internal maxillary artery is contraindicated.[10]

Embolization is a new modality of treatment in uncontrollable epistaxis. By angiography, this technique has the advantage of visualization of the actual bleeding site. In comparison with artery ligation, the abnormal vessels are occluded closer to the site of bleeding, decreasing the likelihood of collateral blood flow causing persistent epistaxis. Because of selectivity, this technique spares as many proximal arteries as possible. Therefore, embolization by the neuroradiologist occludes the vascular system distally and should have the highest success rate.[2,11] In this study, artery ligation after (bilateral) embolization was done in one patient; this was performed at the beginning of this study. The failure may have been a result of insufficient embolic material. At the present time, we would consider performing a second embolization dependent on the first angiographic findings. Therefore, the success rate in our study was 90.9%. In another embolization study, Merland et al,[7] reported a failure rate of 5.9%.

Differing from Davis,[5] we have found that bilateral angiography does not generally seem necessary. It depends on the accuracy of the clinician in pinpointing the bleeding side. Beyond this, recurrence from revascularization develops ipsilaterally.[12] To achieve a permanent occlusion, we used various-sized polyvinyl alcohol particles according to the size of the involved vessels. Although other embolic material was available, we decided to use nonresorbable agents in patients with hypertension and unknown bleedings, since the medical history of these patients revealed frequent recurrences of epistaxis.

The contraindications to embolization include patients with angiographic evidence of dangerous anastomoses and bleeding of ethmoidal arteries, patients with dye allergy, and patients with severe atheromatous disease. The complication rate of embolization in experienced hands is less than 0.1%[7,13]; however, cerebrovascular accidents caused by inadvertant embolization of the internal carotid artery[7,14] and by facial nerve palsy[15,16] have been described.

This new modality of treatment for uncontrollable epistaxis has the advantages of direct angiographic localization of the bleeding site and the fact that the embolization can be carried out immediately after the diagnostic procedure. This not only avoids general anesthetic and surgical procedure in a hemodynamically unstable patient, but it also allows early removal of the choanal pack and more accurate and most distant occlusions of the bleeding vessels.

Postnasal packing creates respiratory compromise and hypoxia by an iatrogenic form of obstructive sleep apnea caused by overfilling of the nasopharynx and depression of the soft palate, especially in elderly patients. Taasan et al[8] demonstrated that choanal packing either caused or worsened sleep-disordered breathing and significantly increased the number, duration, and frequence of obstructive events. Several patients experienced episodes of severe nocturnal oxygen desaturation. Close monitoring of the airway and arterial blood gases is indicated; the removal of the choanal pack as early as possible is a necessity. When posterior packing fails to control epistaxis, early arterial ligation or embolization is essential.

In uncontrollable epistaxis, angiography and therapeutic embolization is most effective in the experienced hands of a neuroradiologist. It should be considered as the method of choice for treatment of severe bleeding that is refractory to anterior and posterior nasal packing. Moreover, embolization therapy should have a primary role in patients with epistaxis caused by defects in the hemostatic system, tumors and vascular malformations[7,9,11] such as Rendu-Osler disease.

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CALCUTTA

The Beneficial Effect of Methylprednisolone in Acute Vestibular Vertigo

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• To assess the efficacy of corticosteroids in acute vestibular vertigo, we randomly selected 20 patients so that half took methylprednisolone and half took placebo. Extensive neurotologic examination confirmed the diagnosis. If no significant reduction of vertigo occurred within the first 24 hours of treatment, patients were instructed to switch medications. Patients were followed up prospectively for 1 month. Of the 10 patients receiving methylprednisolone, 9 had a marked reduction of vertiginous symptoms and 1 switched to the placebo medication. Of the 10 patients receiving placebo, 3 had relief of vertiginous symptoms, while the 7 with persistent symptoms switched to methylprednisolone and had subsequent effective reduction of vertigo within 24 hours. The electronystagmogram returned to normal within 1 month in all 16 patients taking methylprednisolone, but remained abnormal in 2 of the 4 patients treated with placebo. One patient receiving methylprednisolone had a relapse of symptoms when the dosage was tapered, but symptoms again remitted when the dosage was increased to 32 mg/d. From this double-blind, prospective, placebo-controlled, crossover study, we conclude that methylprednisolone is much more effective than placebo in reducing vertiginous symptoms in patients with acute vestibular vertigo.

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After finding cranial polyneuritis in patients with vestibular vertigo (vestibular neuritis, acute labyrinthitis, epidemic vertigo), we reexamined our treatment of bedrest and labyrinthine suppressants. Selected patients with severe nausea and vomiting who required hospitalization were given an intravenous bolus of 100 mg of hydrocortisone sodium succinate or 125 mg of methylprednisolone sodium succinate. The severe symptoms of vertigo, nausea, and vomiting remitted within 6 hours of treatment. These patients were discharged from the hospital within 24 hours of receiving 20 mg of prednisone orally twice a day for 4 days, tapered to 0 over the following 4 days.[1] The rapid reduction of symptoms represents a dramatic improvement over the natural history of vertigo reported to last from days to weeks.[2-6]

Since this initial trial, corticosteroids have become the standard treatment in our emergency department and in the general medical and otolaryngology departments for patients who have acute vestibular vertigo. However, to our knowledge, no article has been published of a clinical trial showing the benefit of short-term corticosteroid therapy in treating acute vestibular vertigo. The objective of this study was to establish whether short-term treatment with corticosteroids would reduce the severity of the vertiginous symptoms or alter the natural course of the disease.

MATERIALS AND METHODS

The beneficial effects of corticosteroids in acute vestibular vertigo have been so well established in the Cranial Nerve Research Clinic at the Kaiser Permanente Medical Center, Oakland, Calif, that withholding steroids from these patients was considered unethical by our Committee for the Protection of Human Rights in Research. As we had determined that the dramatic effects of reducing the clinical symptoms of vertigo, nausea, and vomiting occurred within 6 hours of starting the corticosteroid treatment, we designed a double-blind, crossover study, ensuring that the placebo control subjects would have the opportunity to switch to corticosteroids within 24 hours of starting treatment.

The Upjohn Co (Kalamazoo, Mich) provided tablets of methylprednisolone (Medrol) and placebo, identical in appearance, packaging, and labeling except for code

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Table 1.—Protocol Dosage Schedule of Methylprednisolone (Medrol) in Treating Vestibular Vertigo

Day	Dosage, mg*
1	32
2-4	16†
5	12†
6	8†
7	4†
8	4

*Each pill equals 4 mg.
†Administered AM and PM.

numbering. Methylprednisolone and placebo were paired in bottles labeled 'A' and 'B' and randomized accordingly; of every 10 patients, 5 would start treatment with placebo and 5 with methylprednisolone.

Each corticosteroid tablet contained 4 mg of methylprednisolone, whereas each placebo tablet contained no active ingredient. A trace of quinine sulfate was added to the placebo tablets to impart a bitter taste identical to that of the methylprednisolone.

The diagnosis of vestibular vertigo was based on a history consistent with acute rotatory vertigo suggestive of vestibular manifestations without cochlear involvement. The diagnosis must be supported by pure-tone audiometry within normal limits or bilaterally symmetric, clinically observable rotatory spontaneous or positional nystagmus confirmed by electronystagmography or unilaterally decreased caloric response of greater than 25%. To eliminate the possibility of other neurologic disorders, a general neurologic physical examination was performed along with a thorough otolaryngologic examination, including tests for cranial nerve dysfunction. We tested the trigeminal and upper cervical nerves for sensitivity to pinprick, light touch, and electrical stimulation. The glossopharyngeal nerve was tested by applying a cotton applicator on the posterior aspect of the pharynx to test the ability to initiate the gag reflex. Motor paresis of the laryngeal nerves was determined and confirmed by direct and indirect laryngoscopy.

To be eligible for the study, a patient also had to meet the following criteria: (1) have true vertigo occurring within 72 hours of evaluation; (2) be between the ages of 18 and 65 years; (3) possess enough of an educational background to read, understand, and sign a consent form; (4) agree to take the medication as prescribed and other medications only if approved by the investigators (including another physician's prescription, over-the-counter medication, or medication used before entering the study); (5) have no contraindications to steroid treatment; and (6) agree to return for follow-up tests.

Electronystagmography was performed at the initial visit before treatment and repeated twice, at 1 week and at 1 month after treatment.

Laboratory studies included complete blood cell count with Westergren sedimentation rate, VDRL, automated chemistry panel, and acute and convalescent herpes simplex and herpes zoster virus titers.

Patients took a single 32-mg dose of methylprednisolone orally on the first day of treatment and took divided doses of 16 mg twice a day for 3 days. To preclude the possibility of rebound inflammation by stopping the prednisone abruptly, we elected to taper the dosage to 0 after 8 days (Table 1). If patients taking pills from bottle A had relief of vertigo, nausea, and vomiting, they continued this treatment. However, if no significant relief of symptoms occurred within 24 hours of starting treatment, patients switched to taking pills from bottle B.

Subjective relief of vertigo, nausea, and vomiting was the primary consideration in determining drug effectiveness for each patient. Relief was reported by the patient and recorded by a research assistant without the knowledge of the treating physician. Degree of vertigo was rated on a scale of +1 to +4 and included such parameters as the patient's ability to walk without assistance or drive a car and the presence of nausea or vomiting.

RESULTS

Of the 42 patients referred to the study, 8 were excluded: 4 for recurrent vertigo and 4 for nonvestibular vertigo. Fourteen more patients refused entrance into the study and were treated with an intravenous bolus of 100 mg of hydrocortisone sodium succinate or 125 mg of methylprednisolone sodium succinate, as well as 20 mg of prednisone orally to be taken twice a day and then tapered to 0 during the next 4 days. Thirteen of these patients (93%) had remission of symptoms within 6 hours of starting treatment. The remaining patient had persistent positional vertigo for 4 weeks. Four other patients experiencing a recurrent episode of vertigo were successfully treated with methylprednisolone orally.

Table 2.—Characteristics of Patients*

	Methylprednisolone	Placebo
No. of patients	10	10
Male/female	2/8	5/5
Median age, y	44.1	40.8
Degree vertigo		
+ or ++	5	8
+++ or ++++	5	2
Nystagmus		
Spontaneous	5	5
Positional	8	8
Decreased calorics	3	2
Nausea	6	7
HSV titer >1.8	10	7
Elevated erythrocyte sedimentation rate	5	1

*Plus sign, moderate; double plus signs, moderate to severe; triple plus signs, severe; quadruple plus signs, incapacitating; and HSV, herpes simplex virus.

Table 3.—Effectiveness of Methylprednisolone vs Placebo in Reducing Vestibular Vertigo*

	No. of Patients	
Parameters	Methylprednisolone	Placebo
Decreased vertigo†		
Success	9	3
Failure	1	7
One-month ENG‡		
Normal	16	2
Abnormal	0	2

*ENG indicates electronystagmogram.
†Fisher's Exact Test, *P* = .02.
‡Fisher's Exact Test, *P* = .06.

The initial clinical and laboratory features of the 20 patients entering the study are listed in Table 2. Each group included 10 patients: 2 men and 8 women in the methylprednisolone group and 5 men and 5 women in the placebo groups. No other medications were taken by any of the patients. The median age for the two groups was 44.1 and 40.8 years, respectively. Those in the methylprednisolone group tended to have more severe vertigo. Initial vestibular signs were comparable between the two groups. The majority of patients in both groups had nausea. Nine (45%) of the 20 patients entering the study had signs of cranial polyneuritis, including hypesthesia of the trigeminal nerve, of the second cervical nerve, of the posterior pharyngeal wall (glossopharyngeal nerve), and paresis of the palatine or the superior laryngeal branch of the 10th cranial nerve. There was no apparent response difference between those with or without cranial nerve dysfunction, and the numbers are too small for statistical analysis. No patient had an abnormal complete blood cell count or a reactive VDRL test result. The erythrocyte sedimentation rate was slightly elevated in 6 patients (30%).

All patients initially treated with methylprednisolone and 7 of the 10 patients initially treated with placebo had herpes simplex complement fixation titers more than 1:8. No diagnostic increase occurred in the complement-fixation titers to herpes simplex or herpes zoster virus.

Methylprednisolone was more effective than placebo in reducing vertigo (Table 3). Of those initially treated with methylprednisolone, 90% experienced a decrease in vertigo, compared with only 30% of those initially treated with placebo. All 7 placebo failures switched to methylprednisolone within 24 hours and subsequently had a decrease in vertigo (Fisher's Exact Test; $P = .02$). The 1 patient who switched from methylprednisolone to placebo was not relieved of symptoms.

One patient receiving methylprednisolone had a relapse of symptoms when the dosage was tapered to 16 mg/d. Symptoms remitted again when the dosage was returned to 32 mg/d. Symptoms failed to return following routine tapering of the medication.

The electronystagmogram in all 16 patients taking methylprednisolone returned to normal within 1 month (Table 3). Two of the 4 patients treated with placebo had persistent positional nystagmus (Fisher's Exact Test; $P = .06$). In addition, 1 patient had symptomatic paroxysmal positional vertigo.

COMMENT

Patients with Bell's palsy who also presented with vertigo led to the hypothesis that vestibular vertigo may be a manifestation of viral polyneuritis.[7] This hypothesis was supported by finding cranial polyneuritis in patients with vestibular vertigo.

Acute vestibular vertigo describes a broad group of patients having vestibular symptoms without cochlear deficit.[1] As in any disease, individuals may exhibit from one to all of the spectrum of characteristics that defines the total entity. Separate clinical diseases should not be created based on the arbitrary combination of these characteristics. The division of acute vestibular vertigo into such entities as vestibular neuritis, epidemic vertigo, and acute labyrinthitis represents a semantic difference.

Variables associated with the onset of vestibular vertigo include infection,[8-11] viral illnesses,[4,12-14] febrile illnesses,[10] the onset of menses,[9,15] and even physical and psychological stress.[9,16] Cases of vestibular vertigo should not be categorized based on various triggering factors. The peak incidence of vestibular neuritis is between the ages of 30 and 50 years, suggesting endogenous reactivation of a virus rather than a primary infection.[17] Eighty percent to 90% of adults have antibodies to herpes simplex virus,[17] but even in the face of demonstrable levels of serum antibodies, recurrent infections have been noted.[16]

The finding of increased cerebrospinal fluid protein without evidence of blood-brain barrier damage in patients with vestibular neuritis suggests that demyelination, possibly initiated by viral infection, may be involved in its pathogenesis.[17] The presence of acute transitory multiple cranial nerve dysfunctions in 45% of our patients with vestibular vertigo further supports the concept of inflammatory neuritis or localized meningoencephalitis as opposed to degenerative neuropathy.

Many authors have suggested that herpesvirus may have a role in some episodes of vertigo.[1,17-21] Vertigo has been associated with both herpes simplex[1,15,21-23] and herpes zoster[20,24-26] polyneuritis. Herpes zoster causes a more severe form of polyneuritis, but its pathogenesis is identical to that of herpes simplex virus.[15]

The pathophysiology of the neuronal effects of herpes simplex reactivation readily explains the development of the clinical symptoms of acute vestibular vertigo. Further, herpes simplex virus reactivation and acute vestibular vertigo have been noted to be triggered by similar factors, including exposure to wind or sunlight, fever, menstruation or certain hormones, or severe emotional experiences.[27]

Herpes Simplex Virus

The herpesvirus enters the thin mucous membranes of the respiratory tract and travels up the neuronal axons to the ganglion.[27] Inflammation can extend from one ganglion to another by axon transport.[17] Dissemination of infection by direct cell-to-cell contact is probably facilitated by an alteration in the social behavior of host cells infected with herpesvirus.[28] In the head and neck, the trigeminal, glossopharyngeal, and vagus nerves are the most vulnerable.[7]

During the latent period, the herpesvirus resides in the ganglionic nuclei in a noninfective, nonreplicating form. When triggered by one of many factors, the virus may begin to replicate in the infected ganglion cells.

The infected host cells exhibit new surface immunologic determinants similar if not identical to those present on the surface of the envelope of the virus.[28] An autoimmune reaction around the ganglions may cause localized meningoencephalitis and polyneuritis.[29] Edema of the myelin sheath occurs, followed by infiltration of the peripheral nerve fiber by lymphocytes and plasma cells.[29] Subsequent demyelination impairs nerve function.

Both motor and sensory nerves may be affected. Nerves with cell bodies located in ganglia infected with herpesvirus are hypofunctional, but if inhibitory fibers traversing the ganglion are affected there may actually be hyperfunctional symptoms.

With resolution of the edema and inflammation, remyelination and reestablishment of nerve function occur,[29] which may explain the spontaneous recovery of reduced caloric responses in vestibular neuronitis.[17]

Conclusions and Treatment

We believe that the variability of symptoms associated with vestibular vertigo is due to the randomness of the clinical presentation of polyneuritis. The spectrum of severity may be due to differences in the virulence of the infecting agent, the host resistance, or the degree of lymphocytic and plasma cell infiltrate of the affected neurons.[20,29]

The role of steroids in decreasing edema and inflammation has been well established; they are therefore a logical choice to treat vertigo caused by polyneuritis. Methylprednisolone and hydrocortisone acetate were initially selected for use because of their ready availability in intravenous form that was needed for those patients with concomitant nausea and vomiting. Generic prednisone was used when oral steroids were indicated. Milligram equivalents of each corticosteroid are listed in Table 4. Although no determination of relative effectiveness was attempted, intravenous hydrocortisone acetate was discontinued because a single bolus provided only an equivalent of 20 mg of prednisone.

The effectiveness of methylprednisolone was confirmed by this double-blind, randomized, prospective study.

Vestibular vertigo should not be classified into separate clinical entities based on arbitrary combinations of characteristics that define the total entity, nor on the basis of the variety of triggering factors.

Table 4.—Equivalents of Dosages of Corticosteroids*

Methylprednisolone	Prednisone	Hydrocortisone	Cortisone
4 mg =	5 mg =	25 mg =	20 mg

*To facilitate changing to methylprednisolone from other corticosteroids.

For severely vertiginous patients, we recommend an intravenous bolus of 125 mg of methylprednisolone sodium succinate, followed by corticosteroids, administered orally, equivalent to 20 to 30 mg of prednisone twice a day for 4 days and tapered to 0 during the next 4 days.

For those able to tolerate oral medication, we recommend a loading dose equivalent of 40 to 60 mg of prednisone followed by the above tapering schedule. If symptoms recur when the dosage drops below a therapeutic level, continue the corticosteroid treatment at the initial dose, and then follow the routine tapering schedule.

Acute episodes of vertigo in cases of vestibular neuritis have been noted to last from days to weeks. Treatment with labyrinthine suppressants often requires hospitalization, causes extreme somnolence, and forces the patient to be incapacitated from work. Methylprednisolone dramatically reduces vestibular symptoms, is not sedating, eliminates the need for hospitalization, and allows patients to resume normal activities in a few days, making corticosteroids a cost-effective treatment for vestibular vertigo.

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Editorial Footnote

Because the basic message is similar to that contained in an earlier publication, this article was accepted only after some editorial soul searching. We applaud the use of a randomized, prospective clinical trial to address this complex, challenging issue, and the authors have a unique opportunity to address problems of this nature at their institution. We must remember, of course, that steroids have many potent pharmacologic effects, and we are limited in our ability to characterize the nature of a pathologic process when we are looking only at treatment outcome.

BYRON J. BAILEY, MD
Galveston, Tex

Otitis Media and Hearing Loss In Turner Syndrome

Nancy Sculerati, MD; Jocelyn Ledesma-Medina, MD; David N. Finegold, MD; Sylvan E. Stool, MD

• Twenty-two phenotypic females with Turner syndrome underwent prospective otologic evaluation including a standard history, physical examination, audiogram, and tympanogram. Eight of these patients had computed tomography of the temporal bones. Eighty-two percent of the patients had a history of chronic or recurrent ear infections. Eleven patients (50%) had previous myringotomy and tube placement and 4 (16%) had undergone tympanoplasty or tympanomastoidectomy for sequelae of otitis media. Ten patients (45%) had middle ear effusions evident on examination. Sixteen patients (73%) had hearing loss in at least one ear at the time of examination. Sensorineural losses were evident in 37% of patients. No malformations of the otic capsule were noted on computed tomography. The high prevalence of both hearing loss and otitis media in Turner syndrome warrants otologic and audiologic assessment of patients with this chromosomal anomaly.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:704-707)

Turner syndrome is one of the most common chromosomal abnormalities, affecting about 1 in 3000 live phenotypic female births.[1] Although the anomalies that constitute the Turner syndrome result in a characteristic clinical entity, there is no pathognomonic or diagnostic clinical feature and there is variable expression of the number and severity of abnormalities (Table). Short stature with adult height under 150 cm (5 ft) is the one universal characteristic.[1] An association between chronic recurrent otitis media, hearing loss, and Turner syndrome has been previously reported,[2,3] but otologic and audiologic findings have not been uniform in these reports. The largest series of patients compiled with audiologic data was described by Anderson et al in Sweden.[4] No impedance tympanometric or otoscopic data were reported in those 79 patients. A history of middle ear infections, generally in early childhood, was elicited in 68% of patients. Although this was inferred to be an unusually high incidence by the authors,[4] more recent data show that most normal children (71%) will have had at least one episode of otitis media by age 3 years.[5] Anderson et al[4] noted sensorineural hearing loss (SNHL) with recruitment in 64% of their patients. Polytomography failed to demonstrate any malformation of the inner ear, but cephalograms did demonstrate an abnormal slope of the external auditory canal.

Szpunar and Rybak[6] examined 10 patients with Turner syndrome in Poland and noted that 7 of them had evidence of chronic otitis media, 2 of whom had undergone radical or modified radical mastoidectomy. Mastoid films showed hypocellularity in 9 of their patients. No SNHL was reported in this series.

We prospectively evaluated 22 patients with otologic and audiologic examinations to test the hypothesis that there is an increased prevalence of both otitis media and SNHL in Turner syndrome. Eight of these patients underwent temporal bone computed tomography (CT).

MATERIALS AND METHODS

All patients enrolled by the Endocrine Clinic at the Children's Hospital of Pittsburgh, (Pa) with a diagnosis of Turner syndrome were sent a letter inviting their participation in a "study of the ear in Turner syndrome." Informed consent was obtained from all participants in the study. An examination and hearing test were offered to these patients on the same day as their next scheduled visit. Older patients, no longer actively seen, were invited to participate in the study at their convenience. Patients with Turner syndrome enrolled in the Otolaryngology Outpatient Department, Children's Hospital of Pittsburgh, were also asked to participate.

Participants had a standard otologic history and physical examination performed by an otoscopist whose accuracy in detecting middle ear effusions had previously been validated against findings at myringotomy.

The medical history included questions concerning any recent antibiotic treatment, previous myringotomy and tube placement, tonsillectomy or adenoidectomy, and presence or absence of conditions known to be associated with Turner syndrome (eg, thyroid disease, coarctation of aorta). Detailed questions were asked concerning the age at which ear infections started, their frequency as the child grew, and symptoms associated with these infections. Pertinent family history including socioeconomic data were ascertained. All hospital charts were reviewed.

Physical examination included a detailed checklist of the appearance and mobility of the tympanic membrane on pneumatic otoscopy. Patients were scored on nasal examination according to presence of any nasal exudate, crusting, or evident rhinitis. Oropharyngeal examination was performed to determine presence or absence of a bifid uvula, a high arched palate, any tonsillitis or pharyngitis, and estimation of relative tonsil size.

Pure tone air conduction, bone conduction, and speech recognition thresholds were measured with conventional behavioral hearing tests using the Grayson-Stadler 16 clinical audiometer. Speech discrimination was tested with the W-22 list of phonetically balanced words. A 25-word list was used unless there were more than two errors. Play audiometry (using the Maico MA40) was used for children too young for conventional testing. Electroacoustic impedance was performed with a standard impedance bridge (Madsen ZO73).

Axial and coronal temporal bone CT scans were obtained in 6 consecutive patients. Two additional patients had previous axial scans performed for clinical indications unrelated to the study. All patients

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Presented in part at the 16th annual meeting of the Society for Ear, Nose, and Throat Advances in Children, New York, NY, December 2, 1988.

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were scanned in a high resolution scanner (GE 9800) without contrast enhancement. Axial scans were performed at 1.5-mm intervals through the temporal bones. Limited coronal scans were performed through the external auditory canal.

RESULTS
History and Otologic Examination

A high prevalence of otitis media was found in the study population. Eighty-two percent of families answered "yes" to the question "Were repeated ear infections ever a problem?" Most children of these families had histories of recurrent acute otitis media with associated fever and otalgia. All but two families agreed that the frequency of infections decreased as the child grew older. Despite the predominance of teenagers in the study group (Fig 1), almost half of the patients (45%) had effusions on otoscopy and abnormal tympanograms at the time of examination. Other abnormalities noted on otoscopy included marked tympanosclerosis (3 patients), otorrhea through a patent ventilation tube (1 additional patient), and anterior pars flaccida retraction pocket (2 additional patients).

All of the patients were white, only 1 girl was from a disadvantaged socioeconomic background.

Half of the patients in the series had undergone myringotomy and tube placement and most had multiple sets of tubes placed (Fig 2). Four patients had undergone tonsillectomy (and adenoidectomy) or tonsillectomy alone for frequent ear infections and/or obstructive symptoms.

Sixteen percent of the patients required major otologic surgery for sequelae of chronic otitis media. Two patients underwent tympanoplasty (1 bilateral) and 2 required tympanomastoidectomy (1 bilateral). All 4 of these girls had retraction pockets located in the posterior pars flaccida or posterior superior pars tensa in at least one ear. Three of the 4 patients had ossicular erosion noted at surgery and 2 of them had a cholesteatoma sac identified at the neck of the retraction pocket, giving an overall incidence of cholesteatoma of nearly 10%.

Chart review revealed 1 patient had inflation-deflation eustachian tube function tests through nonintact tympanic membranes before tympanoplasty. There was a high opening pressure (653 mm of water) in an ear with both a perforation and localized atelectasis, and normal resistance, but no dilation in the opposite ear with a dry perforation on swallowing.

Hearing Status

Only 6 (27%) patients in this series had normal hearing, 8 (36%) had pure conductive losses, 3 (14%) had pure sensorineural, and 5 (23%) had mixed losses (see Fig 3 for ear specific hearing status). Sensorineural losses were usually bilaterally symmetric and mild with midfrequency dips at 1 to 2 kHz. There was one unilateral moderate SNHL. Speech discrimination was excellent in the 21 patients tested.

Nasal and Oral Physical Findings

Oropharyngeal examination demonstrated a marked prevalence (72%) of high arched palate. There was one instance of a palpable submucus cleft.

Four patients had evidence of rhinitis on examination, 1 with nasal polyps. Two girls (both without evidence of rhinitis at the time of examination) were receiving maintenance allergy immunotherapy and both had histories of severe middle ear disease. Referral to an allergist had originally been made for further evaluation of chronic otitis media rather than any classic symptoms of allergy.

Temporal Bone Imaging

Temporal bone CT scans were performed prospectively in 6 study patients, including 2 with SNHL. Previous scans of 2 additional study patients, both obtained for preoperative evaluation of chronic ear disease, were included for review. Half of the girls scanned had sclerotic mastoids with soft-tissue density present in middle ear and mastoid air cells, 2 with bilateral involvement and 2 with unilateral (right-sided) involvement. All of these patients manifested otitis media or retraction pocket at the time of radiologic examination. Two of the remaining 4 girls who had normally developed mastoids showed opacification with menisci indicating fluid in the mastoid air cells. Maxillary sinus retention cysts were incidental findings in 2 patients. Normal bony otic capsules were demonstrated in all patients.

Four of the 6 patients who had coronal CT scans showed a downward slope of the external auditory canals (Figs 4 and 5). Eight age- and sex-matched patients who had coronal CT scans for trauma or tumor were used as the control group. None of the control patients' scans demonstrated downward slope of the canals.

Somatic Features of Turner Syndrome*

- Short stature (less than 150 cm [5 ft])
- Shield chest (rectangular shape with widely spaced nipples)
- Prominent pinnae
- Low nuchal hairline
- Brachycephaly
- High arched palate
- Renal abnormalities (horseshoe kidneys)
- Cardiovascular abnormalities (coarctation of aorta)

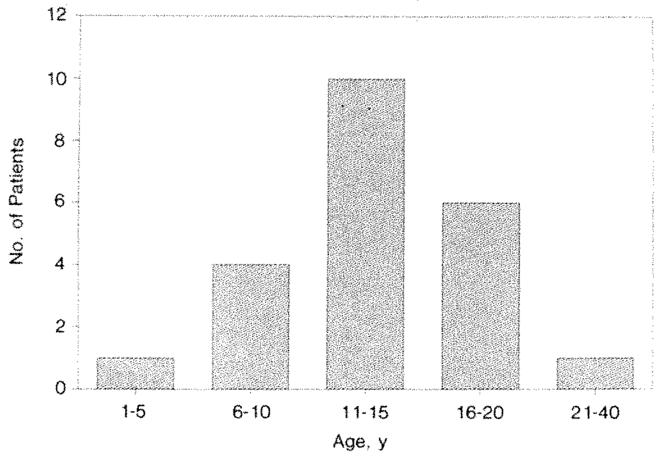
*Modified from Simpson.[2]

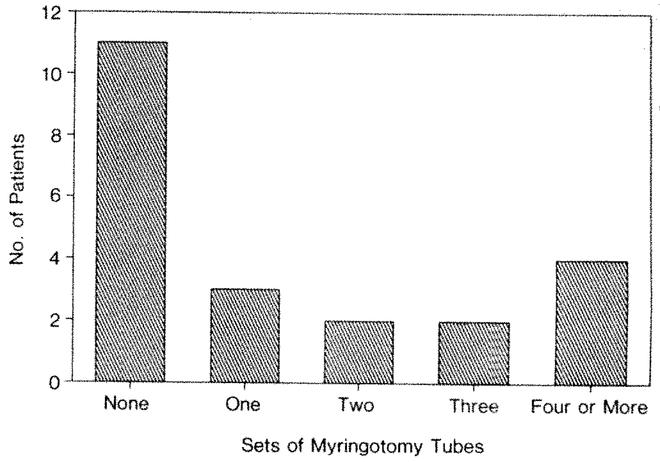
COMMENT

In 1938 an endocrinologist from the University of Oklahoma School of Medicine, Henry H. Turner,[7] described a series of seven young women with the common features of "infantilism" (failure to enter puberty), webbing of the skin of the neck, and an unusual carrying angle of the elbow (cubitus valgus). Later, the endocrine pathology of Turner syndrome was shown to be functional absence of the ovaries. The term *gonadal dysgenesis* remains in use as a synonym for this syndrome.

A normal karyotype contains 44 autosomes and two sex chromosomes; XX in females and XY in males. In 1959, Ford et al[8] demonstrated a complement of 45 chromosomes with monosomy X in patients with Turner syndrome. The syndrome is currently considered to be a phenotypic expression of sex chromosomal deficiency. Portions of the X chromosome rather than the entire second X chromosome are absent in subsets of patients with the Turner phenotype. Less often, there may be a fragment of the Y chromosome paired with the X. Many patients are mosaics who evidence chromosomal abnormalities only in subpopulations of cells. Mosaicism may explain the variability of somatic features in the syndrome.

The findings of a high prevalence of otitis media and hearing loss in patients with Turner syndrome is intriguing in light of the known sex





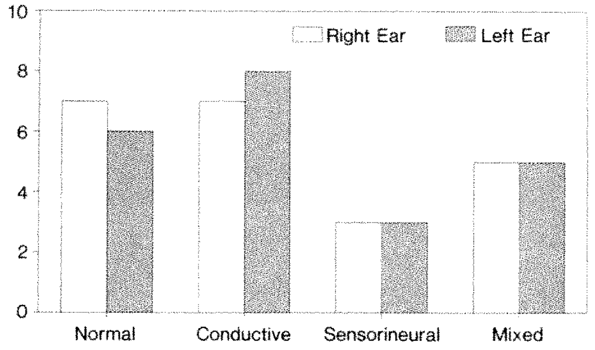


Fig 1.—Top left, Age distribution of the 22 Turner syndrome patients enrolled in the study.

Fig 2.—Top right, Half of the study population underwent myringotomy with tube insertion, more than one third of the patients (36%) had multiple sets placed.

Fig 3.—Bottom left, Ear specific hearing status in 22 patients with Turner syndrome.

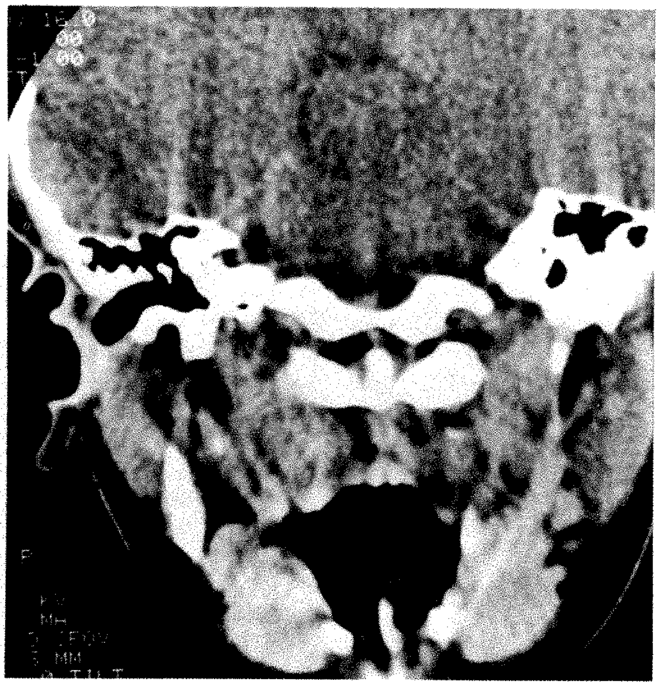


Fig 4.—Coronal scan through the external auditory canal shows the downward slope of the right canal.

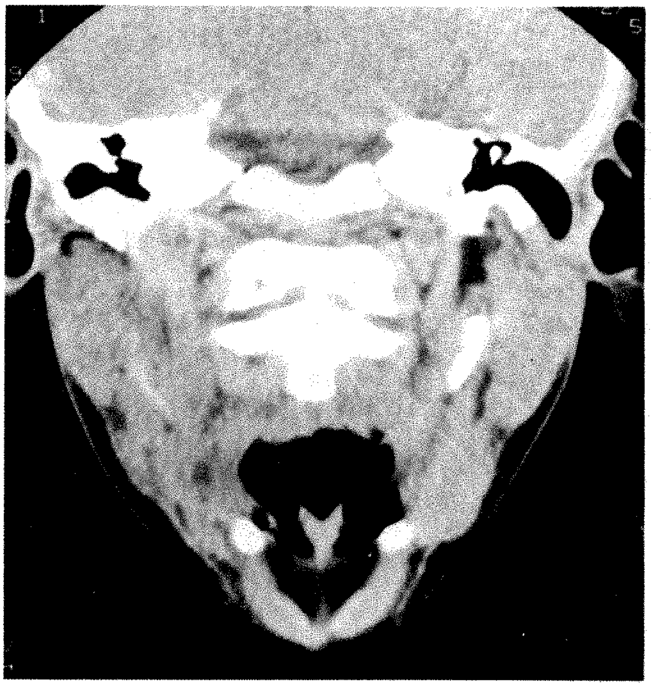


Fig 5.—The left canal shows a similar finding in the scan 3 mm posterior to the image shown in Fig 4.

chromosomal abnormalities in this syndrome.

A representational population of patients with Turner syndrome was sought in this study to further evaluate this reported association. Approximately 80% of patients with Turner syndrome who kept scheduled appointments at the Endocrine Clinic during the tenure of this study chose to become participants. This reflected the usual number of the group previously willing to participate in other clinical studies at the Childrens' Hospital of Pittsburgh. Two of these patients were also followed up by the Otolaryngology Outpatient Department at the same hospital. While the 20 study patients recruited through the Endocrine Department were unselected for ear disease, the 2 patients recruited from the Otolaryngology Department presented with otologic disease.

The results of this study confirm a markedly high prevalence of both otitis media and SNHL in Turner syndrome.

What is responsible for the high prevalence of chronic otitis media? Brachycephaly and high arched palate are associated with Turner syndrome, both have been postulated to account for excessive otitis media in various craniofacial syndromes. Although many cases of high arched palate and 1 case of a submucus cleft were observed in our patients, the presence or absence of palatal abnormalities does not correlate with the presence of middle ear disease in all patients. Four patients with grossly normal palates had histories of excessive otitis media (¾ having had multiple sets of tubes). On the other hand, 2 of the 3 patients in the series with no history of problematic ear infections and normal otoscopic examinations had markedly high arched palates. Brachycephaly was never scored on physical examination because of the imprecision of diagnosis by simple inspection. There was no preferential association found between other organ system abnormalities seen in Turner syndrome (such as thyroid disease or bicuspid aortic valve) and the presence of either hearing loss or otitis media.

Eustachian tube function tests performed in 1 patient with dry perforations before tympanoplasty suggested at least unilateral functional obstruction. This datum represents the first report of eustachian tube function results in a patient with Turner syndrome, and is too limited a basis for generalization.

Although the Y chromosome contains less genetic material than the X chromosome, several genetic loci are apparently paired between the X and Y chromosomes.[9] It is interesting that boys have a higher incidence of otitis media than girls in most epidemiologic studies. Along with our results, this suggests there is a relationship between phenotypic manifestations of sex chromosomal material and the propensity to develop middle ear infections. Future studies correlating individual study patient's specific complement of X-chromosomal material found on DNA analysis with clinical presence of chronic otitis media and/or SNHL are in preliminary stages.

What is responsible for the marked prevalence of hearing loss in patients with Turner syndrome? Paparella et al[10] reported an increased prevalence of SNHL in a large series of patients with chronic otitis media, most of whom had actively draining ears (almost half with cholesteatoma) at the time of audiologic testing. Although chronic or recurrent otitis media may be invoked to explain the presence of SNHL in Turner syndrome, there is no convincing evidence that recurrent middle ear effusions are associated with a markedly high rate of SNHL. Abnormal bone lines were found in 37% of our patients, only 1 of whom had a history of recurrent drainage. None of the patients who had otologic surgery other than myringotomy and tube placement demonstrated SNHL. Two patients with SNHL had other risk factors: viral meningitis in early childhood and a positive family history. Anderson and coworkers'[4] report of recruitment along with an absence of malformation of the otic capsule on standard polytomography or CT suggest an abnormality of the membranous cochlea.

Conductive hearing loss, in contradistinction to SNHL, is obviously associated with otitis media in this series: all patients with conductive losses had either active otitis media at the time of testing or a history of previous tympanomastoidectomy for sequelae of otitis media. No ossicular malformations were noted on tympanotomy or CT.

Two patients found to have significant sensorineural losses did not suspect they had any hearing impairment. It is important for pediatricians and otolaryngologists to realize the strong association between hearing loss and Turner syndrome and to routinely refer patients with Turner syndrome for audiologic assessment.

The high prevalence of otitis media with persistence of active middle ear disease into adolescence and with sequelae of retraction pocket, ossicular erosion, and cholesteatoma is somewhat reminiscent of a cleft palate population. Patients with Turner syndrome treated for middle ear disease require vigilant follow-up examinations and prompt ventilation for localized pars flaccida or posterosuperior pars tensa atelectasis.

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Hospital Readmissions, Otolaryngology, and the Diagnosis Related Group Hospital Payment System

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• An analysis of otolaryngologic patients requiring readmission was conducted at our institution during a 4-year period to determine the number of readmissions per patient and the time between discharge and hospital readmission. Readmitted otolaryngologic patients were found to have had greater hospital resource utilization, financial risk under diagnosis-related group payment, and mortality, compared with those patients not readmitted to our facility. For patients readmitted to otolaryngologic services (21.2% of total otolaryngologic patients), 20.4% of the readmissions occurred within 30 days of hospital discharge. Of these, 39.3% required one hospital readmission, 16.3% required two readmissions, and 46.4% of the patients called for three or more hospital admissions. Clinical factors were identified that resulted in a greater incidence of otolaryngologic readmission. Otolaryngologic patients readmitted to other clinical services were also studied. This analysis leads to the conclusion that inequities exist within the diagnosis related group hospital payment system vis-à-vis otolaryngologic readmissions. The results of these data also demonstrate leverage points in which we will be able to focus outpatient services for otolaryngologic patients requiring readmission and potentially decrease inpatient hospital expenditures in the days ahead.

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Hospital readmissions are usually categorized as patients with high clinical resource utilization, prolonged illnesses, and a poorer recovery rate when compared with hospitalized patients in general. A surprising number of patients require readmission to the facility shortly after the previous hospital discharge.[1] For example, 20.9% of Medicare patients required readmission within 30 days of hospital discharge.[2] The age of diagnosis related group (DRG) payment has been connected with a deterioration in the fiscal solvency of American institutions, an unbundling of services into outpatient delivery, and a growing uninsured population.[3] A substantial database has already accumulated regarding patient characteristics, hospital resource utilization, and economic risk under DRGs.[4] The DRG payment bureaucracy has been hesitant to make any modifications within the payment system even under substantial pressure from various forces.[3] The purpose of this study was to review a large group of otolaryngologic patients who required readmission to an academic medical facility. We analyzed clinical and economic data for this population by both the time from hospital discharge to readmission and the number of times a patient was readmitted during the 4-year study.

PATIENTS AND METHODS

The Long Island Jewish Medical Center (LIJMC), New Hyde Park, NY, is an 805-bed academic medical center located in suburban New York City affiliated with a medical teaching facility. We analyzed all otolaryngologic patients (pediatric and adult) admitted more than once to the LIJMC for a 4-year period (January 1, 1985, to December 31, 1988) and grouped patients into two categories: (1) the period from hospital discharge to readmission, which was further broken into subgroups containing readmissions within 0 to 30 days of discharge, 30 to 60 days, 60 to 90 days, 90 to 180 days, 2 years, and within 3 years; and (2) the number of readmissions to otolaryngologic services, ie, 1, 2, 3, 4, and 5 or more times. Patients admitted to otolaryngologic services, but subsequently readmitted to another clinical service, were also analyzed. Hospital cost per patient was computed for all patients. A DRG prospective "All Payor" analysis was utilized to calculate hospital reimbursement. The LIJMC is an urban teaching hospital under the DRG reimbursement scheme.

A number of characteristics were analyzed for all patients (mean ± SD). These included total hospital cost, profit/loss under DRG payment, hospital length of stay (days), age, DRG weight index, outliers, and mortality. The number of *International Classification of Diseases, 9th revision, Clinical Modification* (*ICD-9-CM*) diagnoses and procedure codes per patient was also computed. Clinical characteristics analyzed included the actual principal diagnosis and procedure codes for each patient. Both hospital length of stay and cost were divided by DRG weight index to obtain a standard measure of hospital resource utilization. Statistical analyses between groups of patients were performed using the analysis of variance, χ^2 test, and/or Student's t test.

HOSPITAL COST METHOD FOR OTOLARYNGOLOGIC PATIENTS

Hospital cost per patient was obtained by utilizing per-patient charge-specific data and converting these charges to hospital costs. Cost-charge ratios developed by our

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hospital accounting division were used to convert charges to costs and measure overall expenses. The following ratios were used for each hospital service category.

Category	Ratio
Room and board	0.75
Laboratory	0.40
Blood (storage, processing, transfusion, and products)	1.15
Pathology	2.42
Diagnostic radiology	0.94
Therapeutic radiology	1.71
Operating room	1.10
Recovery room	1.15
Respiratory therapy	0.76
Electrocardiology	0.25
Electroencephalography	1.40
Medical supplies	1.00
Pharmacy	1.00
Diagnostic ultrasound	0.46
Computed tomographic scan	0.53
Emergency department	0.91
Pulmonary function	0.08

Thus, to obtain the hospital cost for a room-and-board charge of $100, the following calculation was performed: $100 × 0.75 = $75; for laboratory, $100 × 0.40 = $40; for pathology, $100 × 2.42 = $242; and so on. However, cost methods in general are only modestly accurate at assessing the true cost for each hospitalized patient.

RESULTS

Total hospital costs for the 3244 patients analyzed were $10 574 091; the 2557 patients not requiring readmission generated $7 704 981 in total hospital costs, and the 687 patients requiring readmission to otolaryngology generated $2 869 110 in total hospital costs. The distribution of the 687 readmissions by the interval from hospital discharge to readmission is shown in Fig 1. Readmission within 30 days of discharge accounted for 20.4% of readmissions, 17.2% of patients were readmitted between 90 and 180 days of discharge, and 22.1% of patients were readmitted between 180 and 365 days of discharge. The greatest proportion of readmissions (39.4%) required one readmission; 16.3% of patients required two readmissions; and 27.2% of patients required five or more readmissions (Fig 2).

Data on otolaryngology readmissions by the time from hospital discharge to readmission are given in Table 1. The mean age per patient for otolaryngologic readmissions was 21.4 years; nonreadmitted patients were older, 26.5 years ($P < .01$). There was some variation in age by readmission category. The mean DRG weight index per patient was higher for otolaryngologic readmissions (0.7445) compared with nonreadmissions (0.6478; $P < .01$). Readmissions within 30 days of hospital discharge had a higher DRG weight index, 1.28734, compared with other categories. The mean hospital length of stay per patient was higher for otolaryngologic readmissions, 4.50 days, compared with nonreadmissions, 2.97 days ($P < .01$). Readmissions within 30 days of hospital discharge had a higher length of stay, 9.19 days, compared with other categories. The mean total hospital cost per patient was higher for otolaryngologic readmissions, $4176, compared with nonreadmissions, $3013 ($P < .01$). Readmissions within 60 days of hospital discharge had a higher cost compared with other categories. Mortality for hospital otolaryngologic readmissions was higher (0.3%) compared with nonreadmissions, (0.1%; $P < .01$).

Resource consumption (adjusted for DRG weight index) was higher for otolaryngologic readmissions compared with nonreadmissions (Table 2). Mean hospital length of stay per patient was 4.96 days for nonreadmissions compared with 6.95 days for readmissions ($P < .01$). Mean hospital cost per patient was $5144 for nonreadmissions compared with $6651 for readmissions ($P < .01$). The mean number of *ICD-9-CM* diagnosis codes per patient was 1.59 codes per nonreadmitted patient compared with 1.87 per readmitted patient ($P < .01$). The

Fig 1.—Readmissions within 30 days of hospital discharge accounted for 20.4%; within 6 months, 61.6%; and within 1 year, 83.7% of all readmissions.

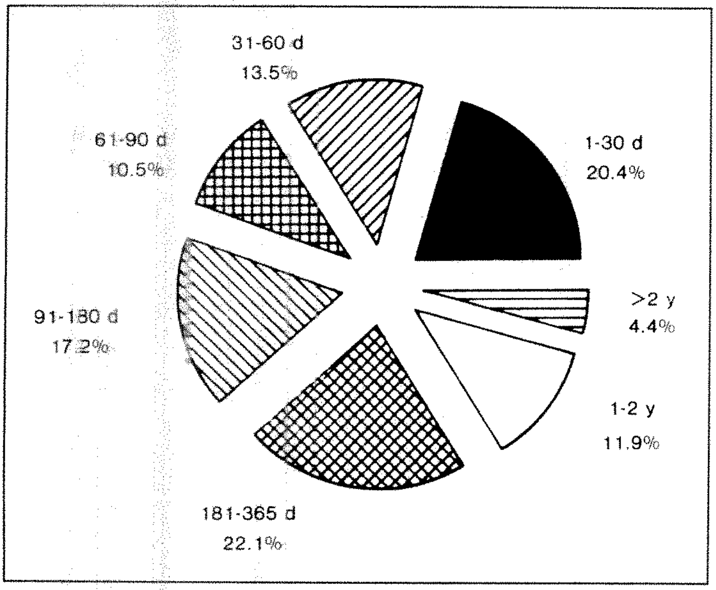

Fig 2.—Times readmitted; 39.4% of patients required one readmission; 33.4% of patients required two to four readmissions; and 27.2% required five or more readmissions.

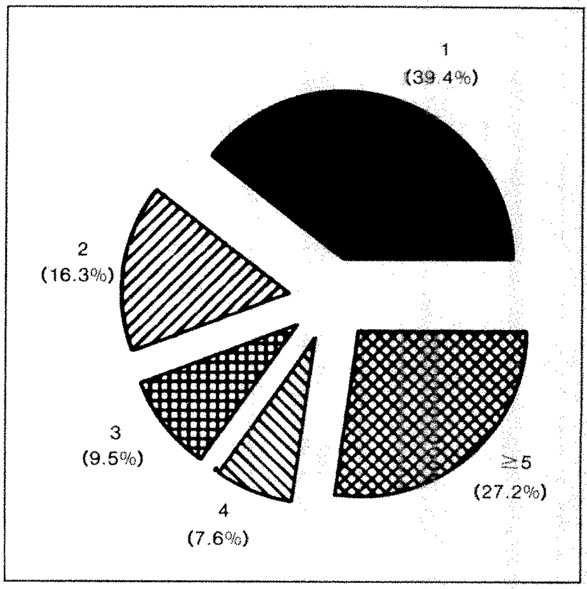

Table 1.—Resource Characteristics for Otolaryngologic Hospital Readmissions by Interval From Hospital Discharge and Times Readmitted*

	Sample Size	Mean Age, y	Mean DRG Weight Index	Mean LOS, d	Mean Cost, $	Mortality, %	LOS/ Weight Index, †	Cost/ Weight Index $†	*ICD-9-CM* Diagnoses	*ICD-9-CM* Procedures	Total *ICD-9-CM* Codes	Outliers, %
Non-readmissions	2557	26.5	0.6478	2.97	3013	0.1	4.96	5144	1.79	1.59	3.39	3.0
Interval, d												
0-30	140	24.7	1.2874‡	9.19‡	8230‡	1.4§	11.12‡	10 128‡	2.56‡	2.14§	4.70‡	19.3‡
30-60	93	20.1	0.6384	5.72	4689	0.0	8.38	7336	2.39	1.94	4.32	12.9
60-90	72	19.6	0.5719	3.25	3024	0.0	6.57	6127	1.99	1.88	3.86	6.9
90-180	118	16.8§	0.5865	3.14	3039	0.0	6.24	6016	1.97	1.79	3.75	6.8
180-365	152	17.2§	0.5280‡	2.57§	2696§	0.0	5.11§	5372	2.01	1.72	3.73	2.6§
2 y	82	26.1	0.7567	2.61	2690	0.0	4.13§	4541§	2.07	1.80	3.88	1.2§
3 y	30	40.5‡	0.6404	2.17	2475	0.0	3.65	4305	1.97	1.70	3.67	0.0
Times readmitted												
1	271	24.4	0.6781	3.27	3229	0.0	5.76	5758	1.89‡	1.65	3.54‡	4.8
2	112	26.5	0.9183	4.85	4284	0.0	6.55	6132	2.12	1.81	3.93	10.7
3	65	27.0	1.2254‡	6.97	6713‡	1.5	7.85	7834	2.60	2.11	4.71	9.2
4	52	17.4	0.6777	3.96	3686	0.0	7.51	6946	2.37	1.81	4.17	9.6
5	187	13.0‡	0.5881	5.39	4739	0.5	8.43	7762	2.41	2.17	4.57	11.2
All readmissions	**687**	21.4	0.7445	4.50	4176	0.3	6.95	6651	2.17	1.87	4.04	8.3

*DRG indicates diagnosis related group; LOS, length of stay; and *ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification.*

†Hospital length of stay and/or cost per patient divided by DRG weight index.

‡Different from mean of all readmissions, $P = .01$.

§Different from mean of all readmissions, $P = .05$.

total number of *ICD-9-CM* codes per patient was also higher (3.39 vs 4.04; $P < .01$). Patients readmitted within 60 days of hospital discharge had the greatest number of *ICD-9-CM* diagnoses and procedure codes compared with other categories. Outliers were higher for readmissions (8.3%) compared with nonreadmissions (3.0%; $P < .01$). Readmissions within 60 days of hospital discharge had the greatest percentage of outliers.

Diagnosis related group hospital payment generated a $1 010 610 aggregate loss for otolaryngologic nonreadmissions (a $395 loss per patient) compared with an $818 165 aggregate loss for otolaryngologic readmissions (a $1190 loss per patient; $P < .01$). All categories of readmissions, except two, generated losses under DRG payment, the greatest loss per patient occurring in those readmitted within 30 days of hospital discharge (Fig 3).

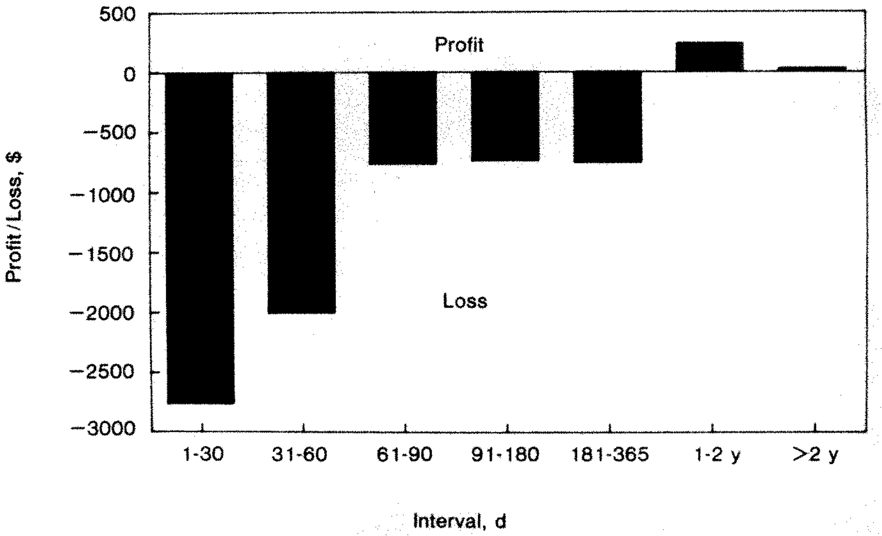

Fig 3.—Readmissions generated an $818 165 aggregate loss; greatest loss per patient was for those readmitted within 30 days of discharge, $2779 loss; five of seven categories generated losses.

Data on otolaryngologic readmissions according to the number of hospital readmissions are given in Table 1. Mean age per patient was highest for patients readmitted three times, 27.0 years. Mean DRG weight index per patient was highest for patients readmitted three times, 1.2254, and lowest for patients readmitted five or more times, 0.5881. Mean hospital length of stay per patient was highest for patients readmitted three times, 6.97 days, and was lowest for patients readmitted once, 3.27 days. Mean hospital cost per patient was highest for patients readmitted three times, $6713, and lowest for patients readmitted once, $3229. Mortality was highest in patients readmitted three times, 1.5%.

Resource consumption (adjusted by DRG weight index) by the number of readmissions required is given in Table 1. Mean hospital length of stay and cost per patient was generally higher for patients readmitted three or more times; longest length of stay was found in patients readmitted five or more times, 8.3 days. The number of *ICD-9-CM* diagnoses, procedures, and total

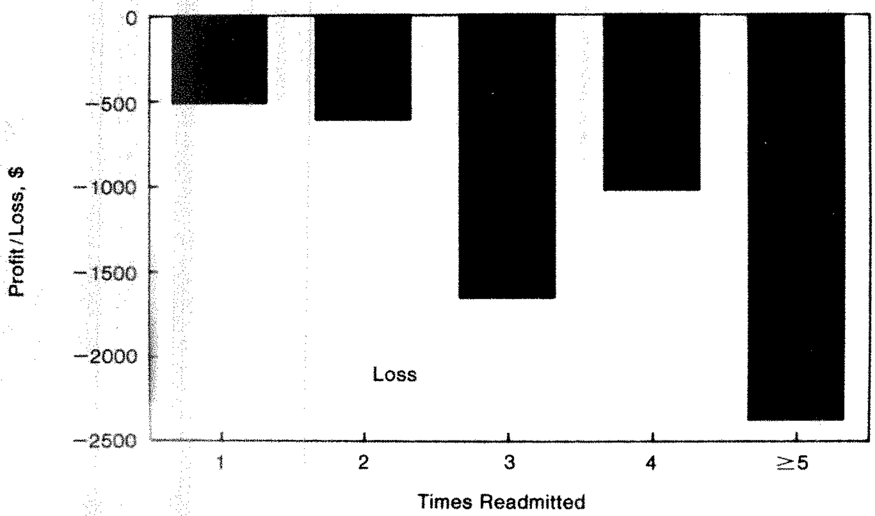

Fig 4.—All categories of otolaryngologic readmissions generated losses; greatest was for patients admitted five or more times.

Table 2.—Resource Characteristics for Nonotolaryngologic Hospital Readmissions*

Interval, d	Sample Size	LOS/ Weight Index	Cost/ Weight Index, $	Total *ICD-9-CM* Diagnoses	Profit/ (Loss), $	Outliers, %	Mortality, %
0-30	30	7.51	5766	7.07	(900)	3.3	0.0
30-60	9	2.27	1883	5.11	5299	0.0	0.0
60-90	7	3.35	2648	4.00	4714	0.0	0.0
90-180	14	6.91	5012	4.50	(1012)	0.0	7.14
180-365	16	5.40	4401	7.50	414	0.0	6.25
2 y	27	5.87	4255	6.26	39	0.0	3.70
3 y	8	6.41	4520	7.75	2394†	12.5‡	0.0
All readmissions	111	5.97	4505	6.31	(253)	1.8	2.7

*Abbreviations are as in Table 1.
†Different from mean of all readmissions, $P = .01$.
‡Different from mean of all readmissions, $P = .05$.

codes was higher for patients readmitted three or more times. Outliers were higher for patients who required multiple admissions; the highest was for patients readmitted five or more times, 11.2%.

Diagnosis related group hospital payment generated losses for all categories of readmissions (Fig 4). Financial was greater in patients readmitted three or more times; it was greatest for patients readmitted five or more times ($2383 per patient). Patients readmitted five or more times generated a $445 650 aggregate loss (54.5% of the total loss from otolaryngologic readmissions). Resource characteristics for the 111 otolaryngologic patients readmitted to other clinical services are given in Table 2. Mean hospital length of stay and cost per patient (adjusted for DRG weight index) were lower for these patients compared with patients readmitted to otolaryngologic services. The mean number of total *ICD-9-CM* codes per patient was 6.31; the mean profit per patient under DRGs was $253; the percent of outliers was 1.8%; and mortality was 2.7%. Thus, these factors were mostly less severe compared with otolaryngologic readmissions in general.

Clinical diagnoses and procedures for readmissions are given in Table 3. The most common diagnoses for patients readmitted to otolaryngologic services were benign neoplasm of the larynx (10.6%), stenosis of the larynx (10.2%), and malignant neoplasm of the larynx (3.1%), whereas the most common procedures for otolaryngologic readmissions were destruction of laryngeal lesion (14.8%); laryngoscopy, tracheostomy, and bronchoscopy (6.2%); and complete laryngectomy (2.3%). For otolaryngologic patients readmitted to other clinical services, the most common diagnoses were maintenance chemotherapy (5.4%), tracheostomy (4.5%) and secondary malignant neoplasm (4.5%); the most common procedures were other laryngeal operation (4.5%), injection of chemotherapeutic agent (4.5%), and unilateral radical neck dissection (3.6%).

COMMENT

The purpose of this study was to analyze otolaryngologic patients requiring readmission to the hospital. It was determined that many otolaryngologic patients required readmission to the clinical facility. These patients had a longer duration of stay and therefore higher costs, a greater severity of illness, and a poorer outcome compared with otolaryngologic patients not requiring subsequent admission to the hospital. These patients also generated a substantial loss to the hospital under the DRG hospital payment method. Patients originally admitted to otolaryngologic services, but readmitted to an alternate clinical service, had an even greater hospital resource utilization than otolaryngologic readmitted patients in general. These findings have implications for both equal distribution and efficiency in upcoming health care delivery.

The federal DRG hospital payment system has been on line for 6 years with no modifications.[5,6] Many hospitals are in financial difficulty owing to this and other factors.[7] Some suggest that the federal and state DRG prospective hospital payment system continues to underreimburse hospitals for the acute care of patients.[8,9] As hospitals receive smaller payment, the fairness of hospital payment becomes the key.

Study has shown that patients who are categorized as minorities; more severely ill; admitted as emergencies; of depreciated socioeconomic status; transferred among hospitals; and very elderly may present hospitals with greater financial risk under DRG payment.[10,11] An analysis by the Prospective Payment Assessment Commission and its report to Congress has shown no major problems in obtaining

Table 3.—Principal Diagnoses and Procedures for Patients Readmitted to Otolaryngologic and Other Services*

ICD-9-CM Code	Sample Size, No. (%)	Description
	Otolaryngologic Service	
Diagnosis		
2121	73 (10.6)	Benign neoplasm, larynx
47874	70 (10.2)	Stenosis of larynx
1619	21 (3.1)	Malignant neoplasm, larynx
1610	14 (2.0)	Malignant neoplasm, glottis
3829	13 (1.9)	Otitis media
74423	11 (1.6)	Microtia
74900	11 (1.6)	Cleft palate
78441	10 (1.5)	Aphonia
1410	6 (0.9)	Malignant neoplasm, tongue
1611	6 (0.9)	Malignant neoplasm, supraglottis
1618	6 (0.9)	Malignant neoplasm, larynx
3879	6 (0.9)	Osteosclerosis
4740	6 (0.9)	Chronic tonsillitis
4785	6 (0.9)	Vocal cord disease
7483	6 (0.9)	Laryngotracheal anomaly
Procedure		
3009	18 (13.0)	Destruction of laryngeal lesion
3323	15 (10.9)	Other bronchoscopy
2001	10 (7.2)	Myringotomy with intubation
0331	8 (5.8)	Spinal tap
8703	8 (5.8)	CT scan of head
3142	7 (5.1)	Laryngoscopy / tracheoscopy
2188	6 (4.3)	Septoplasty
310	6 (4.3)	Injection of larynx
252	5 (3.6)	Partial glossectomy
9904	5 (3.6)	Packed-cell transfusion
2762	4 (2.9)	Cleft palate correction
283	4 (2.9)	Tonsillectomy / adenoidectomy
304	4 (2.9)	Radical laryngectomy
8872	4 (2.9)	Ultrasound, heart
1829	3 (2.2)	Destruction of heart external ear lesion
	Other Clinical Services	
Diagnosis		
V581	6 (5.4)	Maintenance chemotherapy
V550	5 (4.5)	Attention to tracheostomy
19889	5 (4.5)	Secondary malignant neoplasm
V670	4 (3.6)	Surgery follow-up
1509	2 (1.8)	Malignant neoplasm, esophagus
1960	2 (1.8)	Secondary malignant lymph, head / neck
1985	2 (1.8)	Secondary malignant neoplasm, bone
220	2 (1.8)	Benign neoplasm, ovary
2765	2 (1.8)	Hypovolemia
42731	2 (1.8)	Atrial fibrillation
49391	2 (1.8)	Asthma with status asthma
5190	2 (1.8)	Tracheostomy complication
5303	2 (1.8)	Esophageal stricture
65421	2 (1.8)	Preventive C-section NOS-delivery
7991	2 (1.8)	Respiratory arrest
Procedure		
3198	5 (4.5)	Other laryngeal operation
9925	5 (4.5)	Inject cancer chemotherapy
4041	4 (3.6)	Unilateral radical neck dissection
3173	3 (2.7)	Trachea fistula closure
602	3 (2.7)	Transurethral prostatectomy
741	3 (2.7)	Low cervical C-section
9904	3 (2.7)	Packed cell transfusion
3009	2 (1.8)	Destruction laryngeal lesion
4223	2 (1.8)	Esophagoscopy
4224	2 (1.8)	Closed esophageal biopsy
8321	2 (1.8)	Soft-tissue biopsy
8675	2 (1.8)	Revision of pedicle graft
8937	2 (1.8)	Vital capacity determination
9737	2 (1.8)	Remove tracheostomy tube

* *ICD-9-CM* indicates *International Classification of Diseases, 9th revision, Clinical Modification;* CT, computed tomographic; C-section, cesarean section; and NOS, not otherwise specified.

access to medical care related to DRG hospital payment; however, that may change.[12]

Medicare hospital readmissions have been previously shown to account for a substantial portion of the hospitalized population.[2] In addition, factors such as chronic illness and discharge to a nursing home are linked with a greater likelihood of hospital readmission.[13] Recent analysis has also shown that efficiency in the health system can be improved by focusing on the readmitted population. Patients who were expected to have a hospital readmission and underwent targeted outpatient services were shown to have lower inpatient hospital costs.[14] The types of diagnoses and procedures associated with readmission, and how to decrease aggregate costs for this population, will need to be studied in the future.

Reduced health care payments will encourage an improvement in efficiency. The hospital readmission population is likely to undergo much further study. Not only is there financial risk inherent in the DRG hospital payment system for these patients, but it appears that study by disease and type of health care delivery site is likely to offer opportunities for cost containment. Otolaryngologists must analyze the hypothesis presented herein and design ways to deliver cost-effective services in the future.

CONCLUSIONS

A study of otolaryngologic patients was conducted to determine both the number of readmissions and the time between hospital discharge and readmission to an acute care academic hospital over a period of 4 years. Otolaryngologic readmissions accounted for greater hospital resource utilization, financial risk under DRG payment, and fatality, as compared with those patients not readmitted. For patients readmitted to otolaryngologic services (21.2% of total otolaryngologic patients), 20.4% were readmitted within 30 days of hospital discharge; 39.3% required one readmission; 16.3% underwent two readmissions; and 46.4% needed three or more hospital admissions. Clinical elements were identified that yielded an increased likelihood of otolaryngologic readmission. Patients initially admitted to otolaryngologic services but readmitted to other clinical services were also reviewed. Our analysis suggests an imbalance in the DRG hospital payment system vis-à-vis otolaryngologic readmissions. The data also reveal leverage points to focus outpatient services for readmissions and minimize inpatient hospital expenditures in the future.

We would like to acknowledge editorial critique and encouragement in health policy analysis of the late Ira M. Teicher, MD, director of surgical education at LIJMC and governor and fellow of the American College of Surgeons; James Moyer of the Division of Management Information Systems and the DRG Task Force at LIJMC; and to Christina Weiss for the preparation of the manuscript.

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Editorial Footnote

The senior author, who holds an MBA as well as an MD degree, provides some valuable insights into the economic aspects of readmissions for patients with otolaryngologic conditions. His analysis is well researched and well written and serves to confirm suspicions that we have shared on an intuitive level. Older, sicker patients require more readmissions and they are more costly to the system.

Our reviewers were bothered by the general tone of the "Comment" section of the report, because it is possible that others will cite it and use its message for their own purposes. The authors state that the DRG system has been in place for 6 years, with minimal modification, and that its provisions have led to underreimbursement of hospitals. We all know that hospital financing is so precarious in many regions that we are experiencing an unprecedented rate of hospital closings. The problem is particularly serious in rural and underserved urban areas.

We wish that the authors would return to their study and develop specific recommendations for changing federal policy, rather than suggesting that the burden be shifted to physicians to design ways to deliver more cost-effective treatment. If we are to be successful in solving some of these complex problems in hospital financing, there will have to be a new and more cooperative alliance formed among patients, physicians, hospitals, and government. Each party will have to share some of the responsibility for modifying the system so that it serves all parties equitably.

Byron J. Bailey, MD
Galveston, Tex

In Other AMA Journals

AJDC

Are Adolescents Getting Smarter About Acquired Immunodeficiency Syndrome?
John D. Steiner; Gregory Sorokin; David L. Schiedermayer, MD; Timothy J. Van Susteren, PhD (*AJDC.* 1990;144:302-306)

Suicide Attempts Among Adolescent Drug Users
Alan L. Berman, PhD; Richard H. Schwartz, MD (*AJDC.* 1990;144:310-314)

Severe Respiratory Syncytial Virus Infection in Older Children
Jessie R. Groothuis, MD; Carol K. Salbenblatt, RN; Brian A. Lauer, MD (*AJDC.* 1990;144:346-348)

Submental W-Plasty for Correction of 'Turkey Gobbler' Deformities

Tamara K. Ehlert, MD; J. Regan Thomas, MD; Ferdinand F. Becker, Jr, MD

• There are many causes and types of submental contour deformities. One such deformity called a *turkey gobbler,* is caused by an excess of flaccid submental skin and as an isolated defect is seen more commonly in men. We have found that skin excision and a running submental W-plasty for correction of this deformity yields a superior cosmetic result with excellent camouflage of the submental scar. Two cases are illustrated.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:714-717)

Submental contour deformities are of several types and require techniques for surgical correction that address the specific anatomical contributions. Excessive submental fat, a low-lying hyoid bone,[1] a dehiscent and/or redundant platysma, and redundant, flaccid submental skin all produce anterior neck contours that are less than the esthetic ideal. While numerous procedures have been described to correct the double chin or the "pseudo-double chin," which results from excessive fat or irregularities of the platysma, few have addressed the particular abnormality of redundant submental skin commonly called the *turkey gobbler deformity* (Fig 1).

Both men and women may have excessive accumulations of submental fat, a low-lying hyoid bone, or a dehiscent and redundant platysma. However, the problem of excessive, flaccid submental skin independent of, or out of proportion to, other contributions seems to occur more frequently in men. The former may be corrected by standard rhytidectomy, especially with the added modality of submental liposuction, or by a variety of techniques involving resection, imbrication, or plication of the platysma muscle.[2-4]

The turkey gobbler deformity, however, is not usually corrected sufficiently using rhytidectomy alone. In fact, for many men who find this excess skin both cosmetically displeasing and a functional nuisance (tight collars and ties become impossible), a full face-lift is neither desired nor necessary; neither are procedures designed to "tighten up" underlying structures such as the mylohyoid and platysma muscles.

In 1932, Maliniak[5] pioneered the concept of local excision of excessive chin and neck skin. In 1955, Johnson[6] restated the importance of direct surgical excision of submental fat and skin. In treatment of the obese patient with a turkey gobbler deformity, Adamson et al,[7] in 1964, described transverse resection of redundant neck skin in conjunction with routine face-lift, submental lipectomy, and plication of the platysma. His incision resembled an extended thyroidectomy incision lying well below the level of the hyoid bone.

In 1971, Cronin and Biggs[8] used what they called a "T- Z-plasty" for excision of excessive submental fat and skin. This consisted of two horizontal arms, one immediately submental, the other at or below the level of the hyoid bone. These were connected by a vertical bar, after an excision of an ellipse of skin, which was closed with one or, rarely, two Z- plasties, each with arms of 2 cm or more.

Finally, in 1973, Rees[9] described several procedures for correction of excessive submental skin. One involved a T-shaped excision of skin necessitating a vertical incision from the submental crease to the level of the hyoid bone. Another utilized a low thyroid incision with undermining of the entire anterior region of the neck and resection of the excess skin; after this, skin was pulled inferiorly, near the sternal notch. Both of these were advocated as secondary procedures to be performed several weeks after a standard rhytidectomy.

While the above techniques did, to varying degrees, correct the underlying deformity, they involved either ex-

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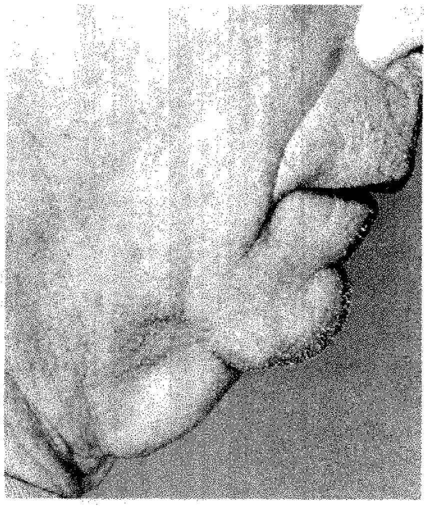

Fig 1.—The "turkey gobbler" deformity.

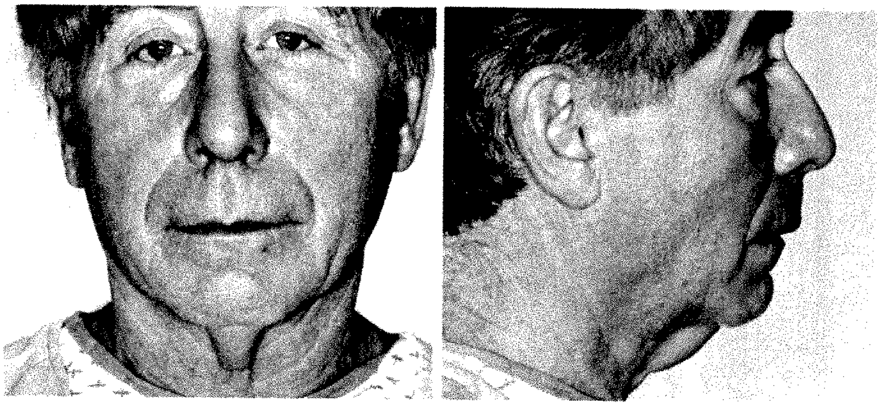

Fig 2.—Preoperative photographs of patient with "turkey gobbler" deformity.

tensive undermining and deep dissection with increased risk of damage to anterior neck structures of scars that were lengthy, low lying, or oriented perpendicular to resting skin tension lines and, therefore, less cosmetically pleasing.

It is our experience that the problem of redundant submental skin, which can occur in men and women but is more often an isolated defect in men, can be corrected adequately using a running submental W-plasty, which gives not only a more concealed scar but one that can most often be confined to an area between the submental and suprahyoid creases.

Procedure

Preoperative, perioperative, and postoperative photographs of one patient are shown in Figs 2 through 4. While still in an upright position, the patient is examined, and the lateral borders of the skin redundancy are assessed and marked. Once the patient is supine, the anterior aspect of the neck is infiltrated with 1% lidocaine with 1/100 000 epinephrine, and a sterile preparation and drape is accomplished. The transverse submental crease is then marked, as is the suprahyoid crease. A W-plasty is outlined vertically, to one side of the midline, along a perpendicular joining these two creases. Each limb of the W-plasty is kept under 1.0 cm in length. Skin undermining is carried out laterally in both directions, with care being taken to confine this to an area that is well below the usual arc of the marginal mandibular nerve. A deep dissection is not performed, but this precaution is still wise in an elective cosmetic procedure.

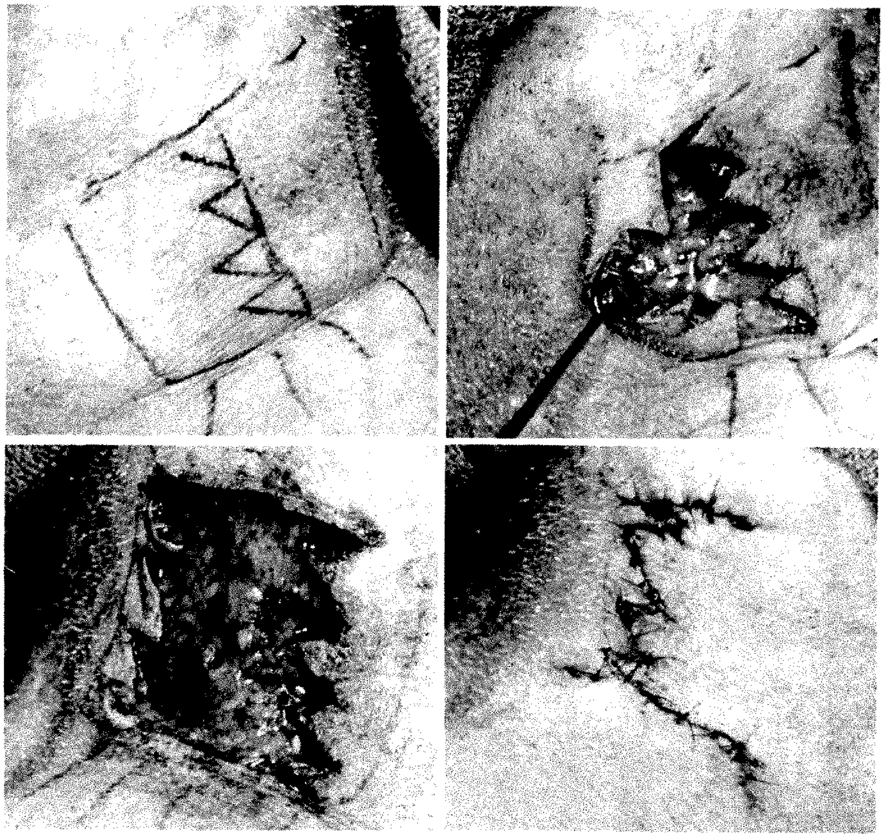

Fig 3.—Procedure for W-plasty correction of "turkey gobbler" deformity. Top left, Skin markings for excision of submental fat and skin. Top right, Lateral undermining of skin for excision. Bottom left, Submental defect after skin excision. Bottom right, W-plasty closure of submental defect.

Excessive submental fat is then resected as necessary but often is not required. If fat is removed, several millimeters are left on the inferior surface of the platysma muscle to allow for uniform skin draping postoperatively.

The previously marked vertical strip of skin is then excised using inferior and superior horizontal incisions in the aforementioned creases, extending only the distance necessary to remove the wedge of skin itself. The W-plasty configuration is, of course, preserved. Hemostasis is achieved using bipolar cautery, and wound closure is accomplished using 5-0 polyglactin 910 (Vicryl) subcutaneous sutures and 6-0 polypropylene (Prolene) interrupted sutures on the skin. The procedure is performed on an outpatient basis, and the patient returns in 5 to 7 days for suture removal.

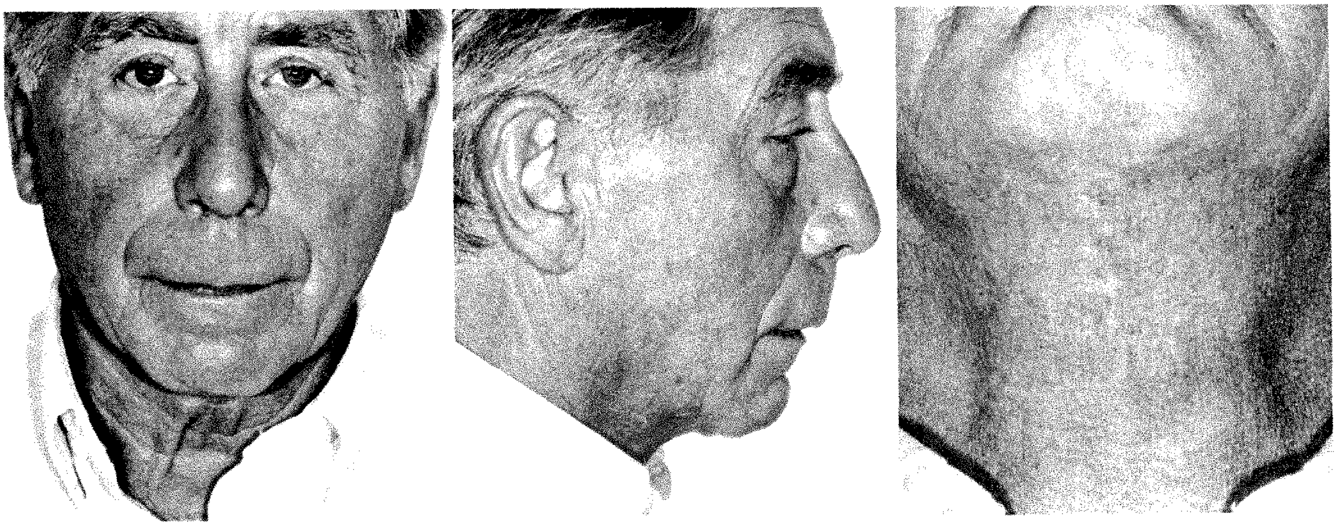

Fig 4.—Postoperative appearance (21 months) after submental W- plasty for "turkey gobbler" deformity. Left, Frontal view. Center, Lateral view. Right, Close-up view of submental scar.

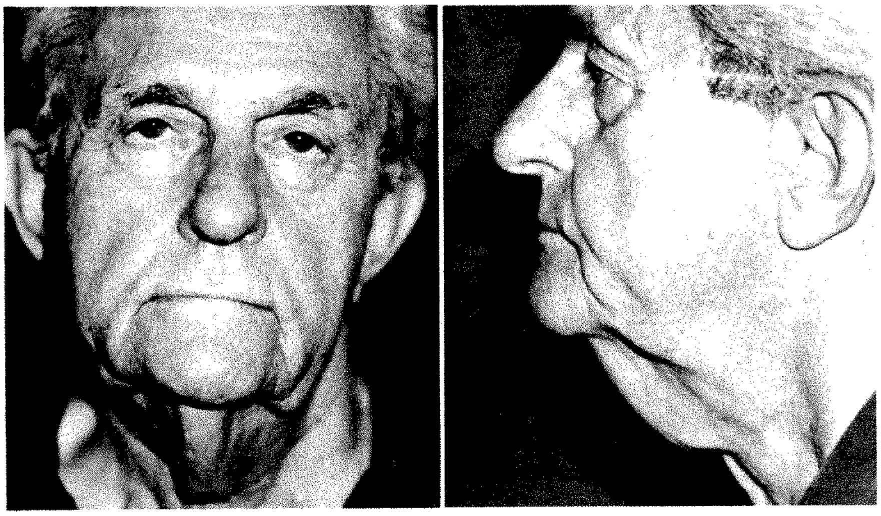

Fig 5.—Preoperative photographs of patient with excessive submental skin redundancy.

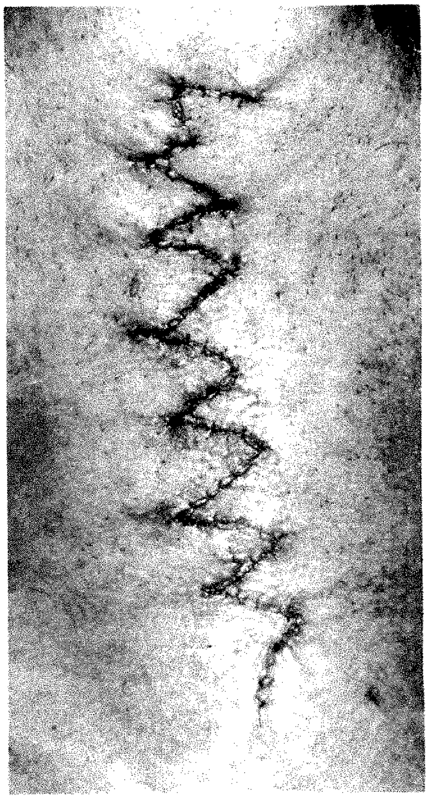

Fig 6.—Running W-plasty closure following excision of redundant submental skin.

RESULTS

After the procedure, the neck skin is quite snug. In older individuals especially, the W-plasty heals with minimal scarring. Eliminating a lengthy vertical scar that is subject to banding and instead using an interrupted W-plasty that lies closer to resting skin tension lines provides a superior cosmetic result. When the incisions can be confined to an area above the suprahyoid crease, added camouflaging is achieved by the shadow of the chin and by the fact that the scar lies in a plane parallel to the floor and is therefore not easily visible from the front. Rarely, in patients with very excessive skin redundancy, the W-plasty is carried below the level of the suprahyoid crease. It is our opinion and that of our patients that in these instances the W-plasty provides adequate camouflage and that a small portion of visible scar is a definite improvement over the preoperative turkey gobbler appearance (Figs 5 through 7).

COMMENT

The running submental W-plasty may be carried out in conjunction with a standard rhytidectomy but is most often applicable to male patients who exhibit exaggerated submental skin redundancy without the associated changes of aging that would warrant a full face-lift. In fact, many men who are distressed by the appearance of the "turkey gobble" and annoyed by the physical discomfort this excess tissue can present are not displeased with the

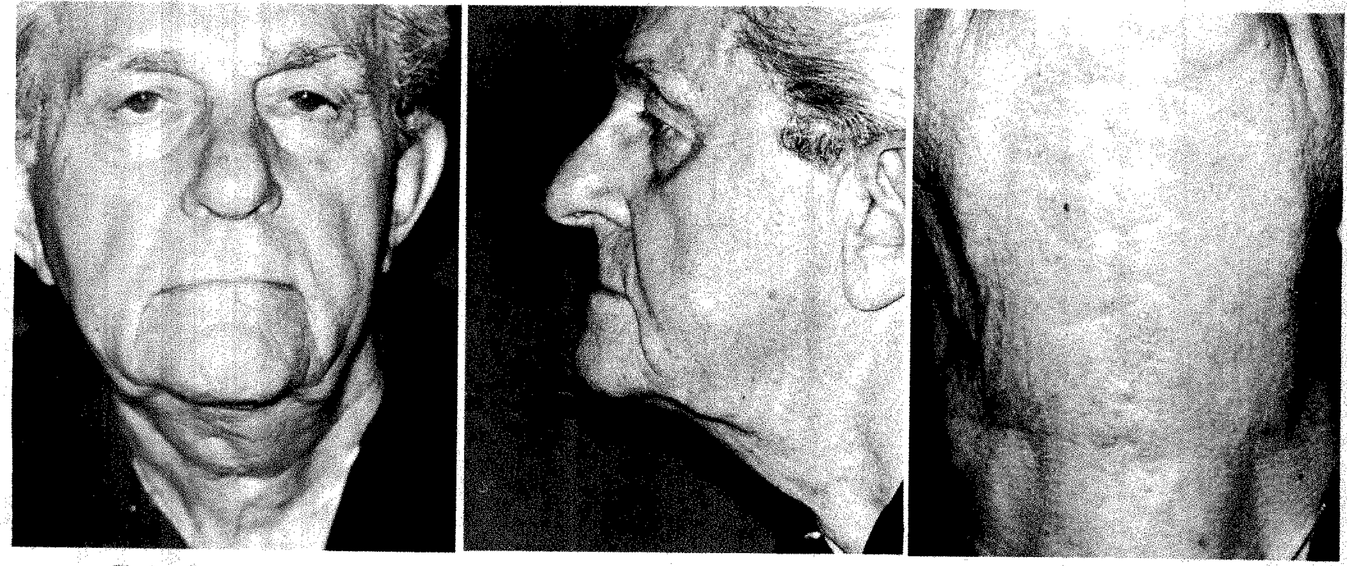

Fig 7.—Postoperative appearance (18 months) after running submental W-plasty for excessive "turkey-gobbler" deformity. Left, Frontal view. Center, Lateral view. Right, Close-up of submental scar.

"mature" look that other facial aging changes impart. It is for these patients that we find the running submental W-plasty most applicable and rewarding. It provides a simple outpatient surgical procedure for correction of an isolated submental contour deformity without the added morbidity of more extensive and, often, unwarranted cosmetic procedures. It does this without leaving an extensive or unsightly scar and is therefore a valuable technique in the repertoire of every cosmetic surgeon.

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Calcified Sphenoid Mucocele

Mika Lidov, MD; Fereidoon Behin, MD; Peter M. Som, MD

• Sphenoid sinus mucoceles are uncommon lesions, and may rarely contain calcifications within their wall. We describe a new appearance of this lesion—sphenoid sinus mucocele with gross calcifications within its matrix.

***(Arch Otolaryngol Head Neck Surg.* 1990;116:718-720)**

Mucoceles are the most common expansile lesions that develop within the paranasal sinuses. Only about 1% of these mucoceles arise within the sphenoid sinuses and, as such, sphenoid sinus mucoceles are rare. Since the first report in 1889 by Berg,[1] there have been to date only about 130 case reports in the literature. It has also been previously reported that only 5% of mucoceles may have macroscopic calcifications, and these occur primarily in the wall of the mucocele.[2] We were unable to find any previous reports of multiple gross calcifications within the substance of mucoceles.

The purpose of this article is to report on a surgically proven case of a heavily calcified sphenoid sinus mucocele. The computed tomographic findings and differential diagnoses are discussed.

REPORT OF A CASE

A 74-year-old woman presented with a 3-week history of ptosis of the left upper eyelid associated with pain in the forehead and left eye. She reported no visual complaints, although 3 weeks prior she had been examined by an ophthalmologist who found her to have a left-sided third-nerve palsy with normal vision. Computed tomographic and magnetic resonance imaging scans revealed an expansile lesion of the left sphenoid sinus that had scattered calcifications (Fig 1). She was then referred to an otolaryngologist whose examination revealed ptosis and medial gaze paralysis in the left eye (Fig 2). She was taken to the operating room for biopsy of the left sphenoid sinus mass. After transnasal approach for sphenoethmoidectomy, submucous resection of the septum revealed a large mucocele containing thick brownish fluid. Culture and sensitivity studies revealed only normal flora. The sphenoid sinus was cleaned and the mucosa was removed completely through an anterior opening in the sinus. Her postoperative course was uneventful, and the patient was discharged with a residual third-nerve palsy that disappeared over the following 6 weeks.

COMMENT

A mucocele is pathologically defined as a collection of mucoid secretions surrounded by a secreting cuboidal epithelium. By this definition, both retention cysts and classic mucoceles are pathologically the same. However, when the clinical and surgical findings of these two entities are studied, these lesions are clearly distinguishable. The retention cyst develops secondary to the obstruction of a minor salivary gland in the sinus mucosa. The epithelium of the obstructed gland and duct becomes the wall of the retention cyst. Such cysts are present in 10% of the population and are usually detected incidentally.[3] A retention cyst rarely fills the entire sinus or causes remodeling of the sinus wall.

On the other hand, a clinical mucocele develops as the result of obstruction to the drainage of a sinus or a compartment of a sinus, with the mucosa becoming the epithelial wall of the mucocele. Mucoceles, therefore, displace the sinus air, totally occupying the sinus, and eventually expanding the sinus cavity. Thus the retention cyst and mucocele are distinct clinical entities that, in the absence of radiographic and surgical data, may appear indistinguishable to the pathologist. It is most likely that some previous reports of sphenoid sinus mucoceles with residual air within the sinus were actually from patients with retention cysts.

Sphenoid sinus mucoceles have an extremely variable clinical presentation that is determined in part by the great variability in the development of the sphenoid sinus within the sphenoid bone, and in part by which of the adjacent structures are affected by the expanding mucocele. The sphenoid sinus is rudimentary at birth and starts its major growth in the third year of life. Pneumatization proceeds inconstantly throughout childhood, and by age 10 to 12 years, the sinus usually obtains its adult configuration.[3] About half of the sphenoid sinuses remain confined to the body of the sphenoid bone, while about half develop lateral recesses and extend into the lesser sphenoid wings, the greater sphenoid wings, or the pterygoid plates. Complete nonpneumatization of the sphenoid sinus is rare, occurring in only 1% of the population, and the lack of any sinus pneumatization by age 10 years should suggest the possibility of "occult" sphenoid disease.[3,4]

Mucoceles tend to extend and expand along the path of least resistance. The sphenoid sinus walls are of variable thickness, depending on the degree of pneumatization, and thus pro-

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vide a variable resistance to the expanding mucocele. The roof of the sinus relates anteriorly to the floor of the anterior cranial fossa and posteriorly to the optic chiasm and sella turcica. The lateral walls are adjacent to the orbital apices, the optic canals, the optic nerves, the internal carotid arteries, and the cranial nerves III, IV, V, and VI within the cavernous sinuses. Posterior to the sinuses are the clivus, the pons, and the basilar artery with the propontine cistern. The floor of the sinus forms the roof of the nasopharynx while the anterior wall of the sinus is the posterior wall of the nasal fossae. The pterygoid canals, transmitting the vidian nerves and maxillary arteries, are usually separated from the floor of the sinus by 1 to 5 mm of bone. However, it is not uncommon to have these neurovascular structures lie completely within the sinus cavity.[5] Thus, depending on the path of mucocele development and which neurological and vascular structures are encroached on, a sphenoid mucocele may have various clinical presentations (Table 1).[6-8]

Patients with sphenoid sinus mucoceles usually have subtle symptoms for several years before a definitive diagnosis is made. The most common presenting symptom is headache, which is most often described as frontal or retro-orbital in nature and is found in roughly 70% of patients.[4,9] The second most common symptom is visual disturbance, which is found in 65% of patients.[8] Most often, patients complain of diplopia, but progression to a complete orbital apex syndrome has been reported in 8% of cases.[6] As the mucocele extends and encroaches on adjacent structures, a variety of symptoms may occur (Table 2).[10-14]

Physical examination is generally unrevealing. A nasal discharge may occasionally be observed or, rarely, a bulge into the nasopharyngeal roof can be seen. Since the sphenoid sinus is by the nature of its location difficult to examine clinically, the diagnosis of a sphenoid mucocele depends primarily on radiological studies. Initially, plain-film studies will demonstrate a completely opacified sinus that may also be expanded. No air margin should be identified between the mucous soft-

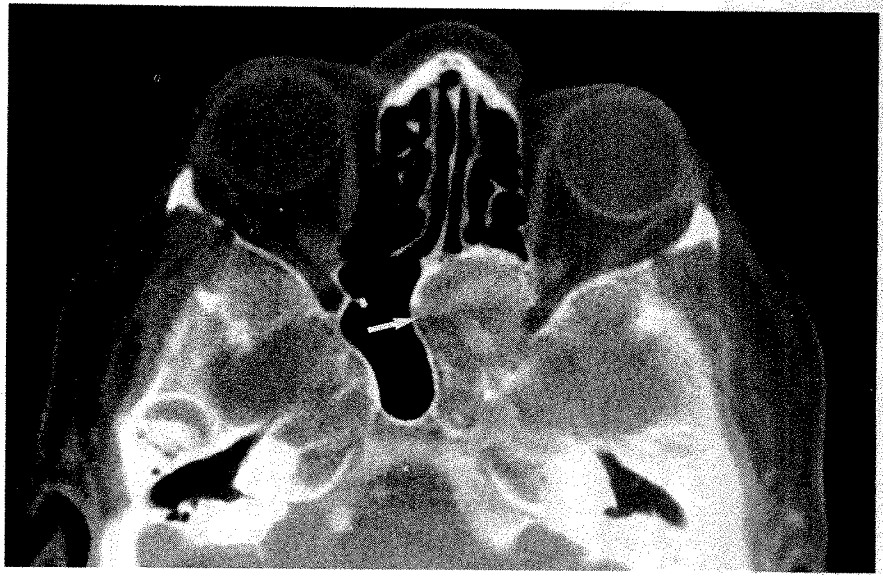

Fig 1.—Computed tomographic scan showing expansile lesion of sphenoid sinus (arrow) with gross calcification.

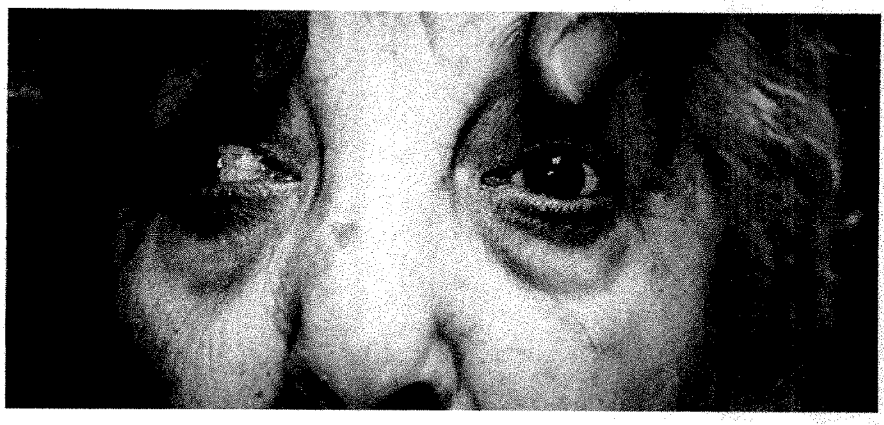

Fig 2.—Physical examination of this patient with a sphenoid sinus mucocele revealed paralysis of medial gaze.

Table 1.—Anatomic Relationships of Sphenoid Sinus

Anatomic Relationship	Anatomic Structure(s)
Superior	Dura Optic nerve (II) and optic chiasm
Posterosuperior	Pituitary gland Sella turcica
Posterior	Clivus Pons Basilar artery (in prepontine cistern)
Lateral	Orbital apex, optic canal, II and ophthalmic artery Cavernous sinus Internal carotid artery Cranial nerve III, Levator palpebrae and oculomotor; IV, trochlear (superior oblique), V, ophthalmic branch, maxillary branch; VI, abducens (lateral rectus) Pterygoid canal (vidian artery, ganglion, and nerve) Maxillary artery
Inferior	Nasopharynx
Anterior	Posterior nasal fossae

Table 2.—Clinical Manifestations of Sphenoid Sinus Mucocele

Cranial Nerve or Anatomic Location	Clinical Findings
Orbit	Orbital cellulitis
Cranial nerve II	Decreased visual acuity or blindness
Cranial nerve III	Ptosis and medial-gaze paralysis
Cranial nerve IV	Paralysis of superior oblique
Cranial nerve V	
Ophthalmic branch	Paresthesia of upper aspect of face
Maxillary branch	Paresthesia of middle aspect of face
Cranial nerve VI	Lateral gaze paralysis
Cranial nerve XII	Deviation of tongue
Pituitary/sella turcica	Decreased libido, amenorrhea

tissue mass and the sinus walls, as such a finding would suggest the alternative diagnosis of a mucous retention cyst. As the accumulating secretions cause progressive erosion of the septations and walls of the sinus, the net loss of bone may cause the expanded sinus to appear relatively radiolucent. Bony sclerosis of the remodeled bony margins can occasionally be seen. Pressure erosion may involve the posterior ethmoid air cells, anterior clinoid processes, optic canals, or orbital walls.

Computed tomography is particularly useful in delineating the full extent of the mucocele.[8] When compared with muscle, depending on the degree of desiccation of its contents, the mucocele may appear hypodense, isodense, or hyperdense. Mucoceles are generally nonenhancing due to their avascular mucoid content, and usually have an attenuation less than muscle, but greater than fat. If, however, the mucocele becomes infected, it is termed a *mucopyocele,* and rim enhancement of the surrounding mucosa is commonly seen. However, such rim enhancement has occasionally been reported in surgically verified mucoceles without evidence of superimposed infection.[15]

Computed tomography is also very useful in characterizing the nature of any adjacent bony involvement and in identifying any subtle areas of bone destruction that would suggest the diagnosis of a carcinoma. This is important because a tumor can cause the obstruction of the sinus ostia that results in the formation of the mucocele. The computed tomographic identification of coexisting tumor and mucocele has been previously reported.[9]

Calcification within a mucocele is rare. It has been previously reported that about 5% of mucoceles show macroscopic calcification, and that rarely these calcifications may be dense enough to simulate an osteoma on plain film.[2] However, these calcifications are described as being peripherally placed within the wall of the mucocele. Our review of the literature revealed no previous case report of a mucocele that had multiple gross calcifications within the mucoid substance of the lesion, as seen in this case.

The main differential diagnosis of an expansile lesion of the paranasal sinuses, which has deposits of calcifications within it, is of a fibro-osseous lesion such as fibrous dysplasia or ossifying fibroma. Fibro-osseous lesions of the paranasal sinuses are not uncommon, accounting for the second largest category of nonepithelial tumors of the sinuses.[16] Fibrous dysplasia may present with monostotic involvement of the calvarium or facial bones and has very rarely been reported to present as an isolated lesion of the sphenoid sinus.[9] Other fibro-osseous lesions of the paranasal sinuses include ossifying fibroma and cementifying fibroma, which are distinguishable only histologically from fibrous dysplasia. Fibro-osseous lesions are typically expansile and usually have a hyperdense or "ground glass" matrix. Foci of calcification or ossification may be seen within the matrix. Ossifying fibroma and cementifying fibroma are benign lesions, but sarcomatous transformation has been reported to occur in fibrous dysplasia involving the sphenoid sinus.[9]

In conclusion, a mucocele is the most common cause of an expanded sphenoid sinus, but it is, overall, an uncommon lesion. Because the sphenoid sinus is clinically inaccessible and because the clinical presentation of a sphenoid mucocele is variable, the diagnosis is primarily dependent on radiographic evaluation. Computed tomography will demonstrate an expanded sinus of variable density, will exclude destructive bone changes suggestive of carcinoma, and will delineate the extent of the process preoperatively. The case presented herein describes a previously unreported appearance of this lesion.

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Fiberscopic Estimation of Vocal Fold Stiffness In Vivo Using the Sucking Method

Shinzo Tanaka, MD, Minoru Hirano, MD

• We developed a fiberscopic device for estimating vocal fold stiffness in vivo. A small plastic tube with a hole in the side was connected to the forceps channel of the fiberscope and used as an aspiration tube under constant negative pressure. A basic experiment revealed that the maximum distance at which the vocal fold was sucked to the hole depended on the stiffness of the tissue. A preliminary study was conducted with a normal subject and four patients: one with sulcus vocalis, one with Reinke's edema, and two with carcinoma. The stiffness estimated using this method was 3 to 4 g/cm for the normal vocal fold. The stiffness for carcinoma and sulcus vocalis was significantly greater than that of normal vocal fold tissue. The stiffness of Reinke's edema did not differ markedly from that of normal tissue.

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Stiffness of the vocal fold tissue is an important factor in voice production. It usually increases in individuals with carcinoma and other neoplasms, scar formation, and sulcus of the vocal fold. The stiffness of human vocal fold has been measured in excised larynges by some investigators.[1-3] However, measurement in vivo has not been possible for technical reasons. Isshiki[4] used a sucking tube for evaluating the plasticity of vocal fold mucosa in an excised larynx. The results of his investigation suggested that the distance at which the mucosa of the vocal fold was sucked to the tube might be a good estimate of the stiffness. The purposes of this article are to discuss the sucking method from a theoretical point of view, to present results of an experimental study of the sucking method, and to show some preliminary results of clinical application.

THEORETICAL BACKGROUND

The vocal fold is displaced when it is depressed or retracted by a small force. When the force is removed, the vocal fold is replaced. Thus, the vocal fold can be regarded as an elastic body in terms of biophysics. The simplest expression of elasticity is the ratio of the force to the displacement. This ratio is constant for an ideal elastic body such as a spring. In this investigation, the stiffness is defined as the ratio of force to displacement. Table 1 shows the stiffness of the vocal fold reported in two previous studies with excised human larynges. The stiffness varied in different conditions of muscle contraction and between the reports. However, the values suggest that the stiffness of the normal vocal fold is below 20 g/cm within a small displacement of the vocal fold.

When the vocal fold is aspirated at a distance, whether or not the vocal fold tissue can be sucked depends on the aspiration pressure and the distance. Figure 1 shows a schematic representation of the reaction of the vocal fold against suction by a constant negative pressure. The vocal fold is expressed as an elastic body. If the distance between aspiration tube and vocal fold tissue is long, the attraction force due to sucking is very small. In this case, the vocal fold tissue is not sucked but approximated to the place where the attraction force is equal to the restoration force of the tissue (Fig 1, center). As the distance becomes short, the attraction force increases. When the distance is short enough for the attraction force to be greater than the restoration force, the vocal fold tissue is sucked to the tube (Fig 1, bottom). Thus, the maximum distance at which the vocal fold tissue is sucked decreases as the restoration force increases. Since the restoration force is proportional to the stiffness, the maximum distance becomes short as the stiffness of vocal fold tissue increases. Therefore, the longest distance at which the vocal fold tissue is sucked to the aspiration tube can be a good index of stiffness. It will be called the *maximum suction distance* in this article.

For application of the sucking method to clinical examination, the following problems should be addressed: (1) What area of the vocal fold tissue is attracted by sucking? (2) What is the relationship between the maximum suction distance and the stiffness of the vocal fold tissue? (3) Do the surface shape of the vocal fold and the heterogeneity of stiffness in the vocal fold tissue influence the result of examination? The first problem can be handled in a basic experiment without human vocal fold. The second problem can be solved with the assumption that the stiffness of vocal fold tissue is constant within the range of small displacement. These two problems will be discussed in the next section. The last problem is important clinically, since most pathologic vocal folds are not homogeneous in structure. It is, however, difficult to solve, because the relationship between sucking force and surface shape and that between total and partial stiffness are unknown. This problem will be discussed further.

BASIC EXPERIMENT

The purposes of the basic experiment were to determine the effective area of the

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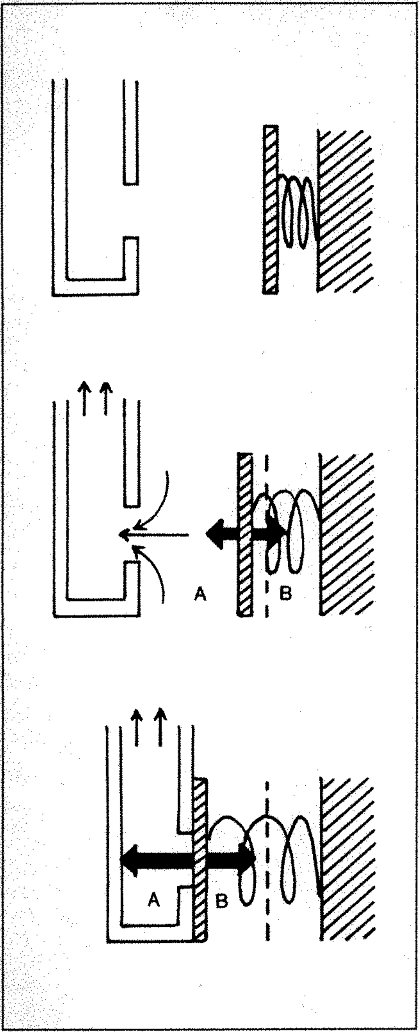

Fig 1.—Schematic representation of reaction of vocal fold to suction. Top, Suction tube and vocal fold without suction. Center, Suction at long distance from the vocal fold. Bottom, Suction at short distance from the vocal fold. A indicates attraction force due to suction; B, restoration force of vocal fold.

Table 1.—Stiffness of Human Vocal Fold in the Mediolateral Direction

Condition of Vocal Fold	Displacement, mm	Force, g	Stiffness g/cm
Without muscular activity*	1	0.13	1.3
	2	0.74	3.7
With cricothyroid muscle contraction*	1	1.26	12.6
	2	3.47	17.3
Not described†	1	1.74 ± 0.42	17.4 ± 4.2

*Calculated from experimental data by Hirano.[1]

†Calculated from experimental data by Kaneko et al[3] for seven subjects. Data for force and stiffness are means ± SDs.

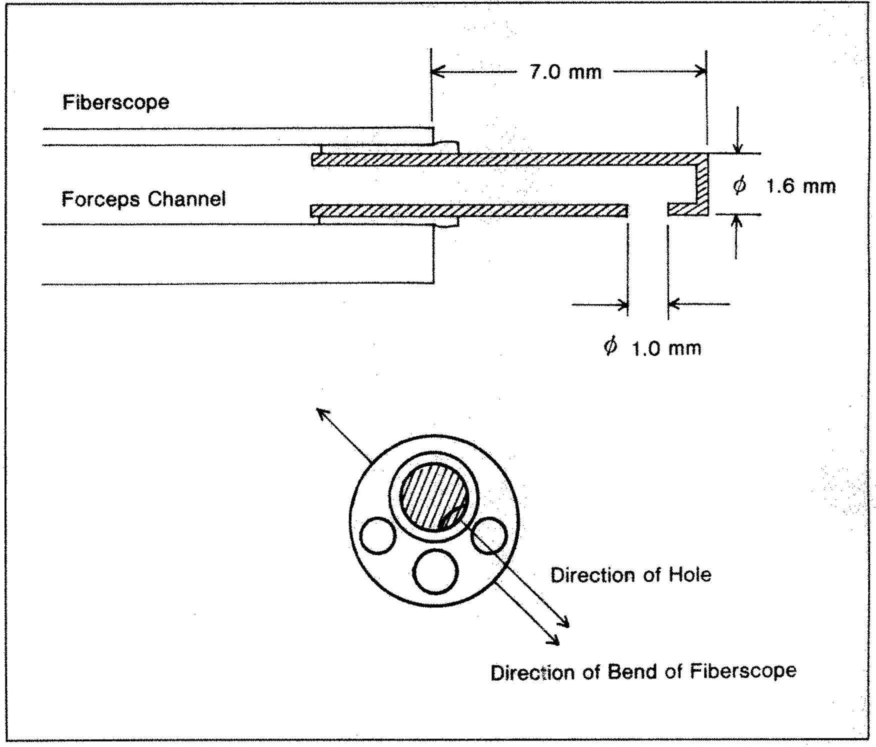

Fig 2.—Suction tube connected to fiberscope.

sucking device employed in the present study, to relate the maximum suction distance to attraction force, and to determine the relationship between the maximum suction distance and the stiffness of the vocal fold for clinical application.

Materials and Methods

As shown in Fig 2, a plastic tube was connected to the forceps channel of a fiberscope (Pentax FNL-K1). The diameter of the tube was 1.6 mm, and it had a hole 1.0 mm in diameter at the side wall. The tip of the tube was closed. The direction of the hole was parallel to the direction of the bend of the fiberscope tip. The forceps channel was connected to an aspirator. The aspiration pressure was kept constant at −400 mm Hg when the hole was opened.

To measure the attraction area and force, cylinders of various diameters and weights were sucked against gravity with this equipment. Each cylinder was made of paper, placed on a horizontal plate, and sucked from above. The diameter of the cylinder was 3 mm, 5 mm, or 7 mm. The weight of the cylinders ranged from 5 to 100 mg for each diameter. The maximum suction distance was measured three times for each cylinder and the average value of the three measurements was adopted. In this experiment, the weight of the cylinder was equal to the attraction force of suction at the maximum suction distance. From the relationship between the weight and the maximum suction distance, the relationship between the stiffness of vocal fold tissue to be investigated and the maximum suction distance was theoretically calculated.

Result

Figure 3 shows the relationship between the maximum suction distance and the weight of the cylinder for different diameters of cylinder. The longest distance was 2 mm, which was obtained for the lightest cylinder (10 mg). The shortest distance was 0.3 mm, obtained for the heaviest cylinder (95 mg). There were no significant differences in relationships between distance and weight among the three different diameters of the cylinder. Thus, the attraction force caused by sucking with this device was supposedly concentrated within a circle 3 mm in diameter. A regression curve was calculated from the values of distance and

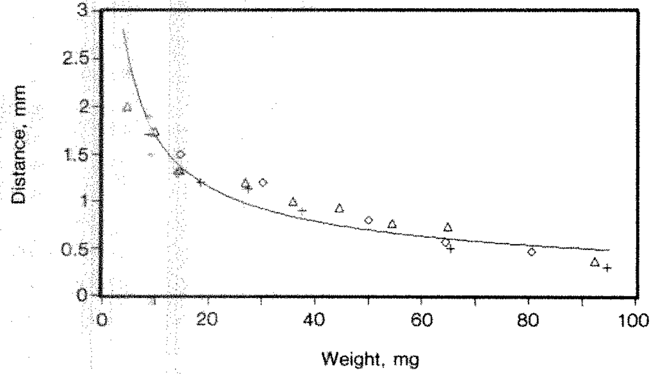

Fig 3.—Relationship between weight of cylinder and maximum suction distance. Triangles, diamonds, and crosses indicate cylinders 3, 5, and 7 mm in diameter, respectively. A regression curve is drawn.

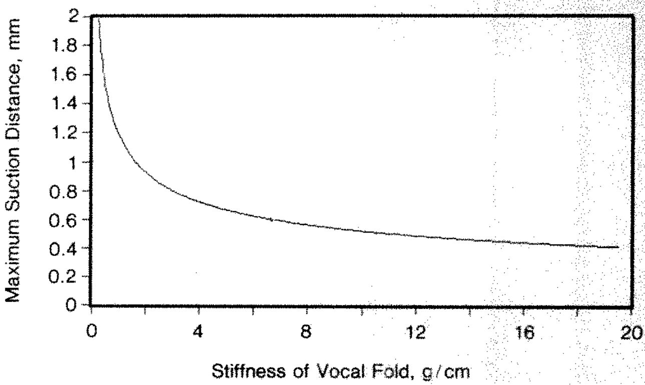

Fig 4.—Relationship between vocal fold stiffness and maximum suction distance.

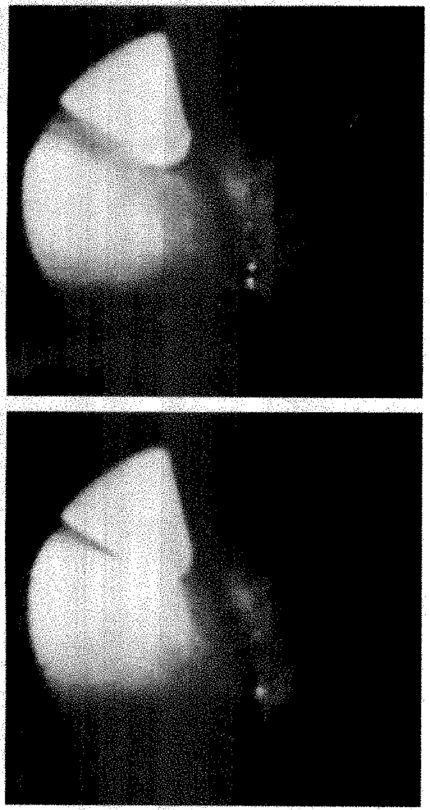

Fig 5.—A pair of images immediately before (top) and after (bottom) the vocal fold tissue was sucked. Duration between images was 0.033 seconds.

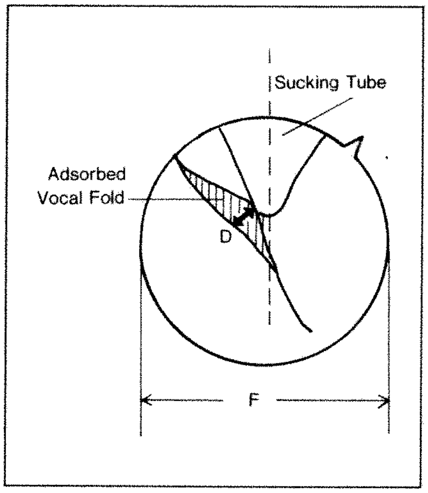

Fig 6.—Measurement of maximum suction distance (D) by superimposing the two images in Fig 5. Angle and magnifying power of D was determined by the location of the suction hole and the field of scope (F).

weight. It indicated that the product of the weight of the cylinder and the maximum suction distance raised to the 1.8th power was constant. In other words, the attraction force of suction was inversely related to the distance from the tube raised to the 1.8th power.

Assuming that the stiffness of vocal fold tissue is constant in the range of displacement of 2 mm or less, the relationship between the maximum suction distance and the vocal fold stiffness can be determined from the regression curve. As the regression curve shows the attraction force at a distance and the restoration force is given by the stiffness and the displacement from this distance, the stiffness in which the restoration force equals the attraction force at any displacement is determined. In this stiffness, the distance is the maximum suction distance. Figure 4 shows the relationship between stiffness and maximum suction distance obtained in this way.

PRELIMINARY CLINICAL APPLICATION

Method

We used the same equipment as in the basic experiment (Fig 2). Following surface anesthesia of the nasal cavity, pharynx, and larynx, the fiberscope was inserted through the nose into the larynx. The object lens of the fiberscope was connected to a video camera (Hitachi DK-5050) and the movement of vocal fold tissue caused by suction was recorded on videotape with a video recorder (Sony VO-5800). Controlling the bend of the tip of the fiberscope, the hole of the tube was approximated to the vocal fold edge at a right angle. The velocity of the approximation was kept as slow as possible so that the approximation could be distinguished, on video image, from the movement of the vocal fold caused by sucking. A pair of video images, one taken immediately before suction of the vocal fold and the other immediately after the suction, was obtained with a video printer (Hitachi VY-100). Figure 5 shows a pair of video images obtained in this way. Superimposing the two images, the maximum suction distance was determined as indicated in Fig 6.

A normal adult subject and four patients with various lesions of the vocal fold were examined.

Results

Table 2 indicates the maximum suction distance and the stiffness for each subject. The stiffness was estimated from the maximum suction distance and the relationship between distance and stiffness shown in Fig 4. In a normal subject, the stiffness denoted the value from 3 to 4 g/cm at the middle and posterior third of the membranous vocal fold. This value roughly agreed with the value obtained for an excised human vocal fold shown in Table 1. In a case of Reinke's edema, the stiffness of the lesion was almost the same as that in the normal subject. The patient with sulcus vocalis and those with glottal carcinoma had significantly higher stiffness of the lesion. Even at the unaffected portion of the vocal fold, the stiffness was slightly greater in the cases of

Table 2.—Maximum Suction Distance and Stiffness by Subjects

Subject	Age, y/Sex	Location of Examination	Maximum Distance, mm	Stiffness, g/cm
Normal	58/M	Middle of membranous vocal fold	0.74	3.7
		Posterior third of membranous vocal fold	0.76	3.4
Sulcus vocalis	61/M	Affected portion	0.33	>20
		Unaffected portion	0.60	6.7
Reinke's edema	37/M	Affected portion	0.79	3.1
Glottal cancer (T1b)	62/M	Affected portion	0.32	>20
		Unaffected portion	0.65	5.4
Glottal cancer (T3)	58/M	Affected portion	0.33	>20

sulcus and carcinoma than in the normal subject.

COMMENT

Significance of Fiberscopic Estimation of Vocal Fold Stiffness

A large glottal gap, an abnormal mass on the vocal fold, and a marked increase or decrease in stiffness of the vocal fold tissue can cause disturbed voice production, as reported by some researchers.[5,6] Among them, the existence of gap or mass is easily confirmed with laryngoscopy or laryngeal fiberscopy. In contrast, the increase in stiffness cannot always be estimated with visual examination. Stroboscopy is a useful examination to estimate the stiffness of vocal fold lesions.[7] The stroboscopic information, however, is qualitative.

Experimentally, the stiffness of the vocal fold tissue has been quantitatively measured in excised human larynges as described previously. The method was based on the direct measurement of vocal fold displacement under weight. It cannot be applied to measurements in vivo. The fiberscopic device with the sucking method employed in this study has a great advantage in measurements of vocal fold stiffness in vivo. This advantage results from the following factors: (1) the small size of the suction tube, which easily reaches the vocal fold; (2) a slight reflective movement of the vocal fold before the vocal fold tissue is sucked to the tube; (3) a side hole in the suction tube, which creates suction of the vocal fold tissue at a right angle; and (4) utility of a video printer for analyzing the fast movement of vocal fold tissue during suction.

Measurements of the stiffness of the vocal fold tissue in normal and varying pathologic conditions will provide important information to investigate the mechanism and dynamics of vocal fold vibration in normal and disease states. They may provide clinically relevant information, including an estimate of the extent of scar formation and subepithelial carcinomatous invasion.

Accuracy of Examination

There are some factors that influence the accuracy of fiberscopic estimation of stiffness. These factors can be classified into four categories: (1) those related to the direction and range of suction force, (2) those related to the surface shape and heterogeneous stiffness of vocal fold tissue, (3) those related to the estimation of stiffness from the maximum suction distance, and (4) those related to the accuracy in determining the exact location for measurement on the presuction fiberscopic image.

As for the direction and range of suction force, we clarified that the suction force was concentrated within a circle 3 mm in diameter when a suction hole 1 mm in diameter and an aspiration pressure of 400 mm Hg were applied at a right angle. The range of suction force may differ for different sizes of the suction hole, for different aspiration pressure, and for different angles. Since the suction force acts only on the surface of the vocal fold, the shape of the surface and the heterogeneity of stiffness of the vocal fold tissue influence the results of the sucking method. When the surface of the vocal fold is uneven, the portion of the vocal fold nearest to the suction hole is most strongly attracted. An increase in stiffness of deeper layers of the vocal fold may shorten the maximum suction distance and increase the value of estimated stiffness. Further studies are necessary to solve this problem.

To estimate the stiffness from the maximum suction distance, it was assumed that the stiffness was constant within a small displacement of vocal fold tissue in this study. The range of displacement in which the stiffness is constant should be determined in the future. As for the location of measurement on the presuction image, it was accurately determined by superimposing the presuction and postsuction images and by observing motion images closely and repeatedly.

Given all these possible factors that can influence the accuracy of estimation, the results of the preliminary studies with living human subjects were within a reasonable range: the estimated stiffness of normal vocal fold roughly agreed with the results of some studies with excised larynges, and the estimated stiffness of glottal carcinoma and sulcus vocalis was greater than that of normal vocal fold. The suction method, therefore, will be a useful technique in estimating the stiffness of the vocal fold in vivo.

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Epiglottic Dysfunction After Isocyanate Inhalation Exposure

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• Epiglottic dysfunction due to environmental exposure is a well-known entity. The most common causes of epiglottic dysfunction include trauma (thermal, chemical, and blunt), infection, allergy, neoplasm, and neurologic disorders. We report an unusual case of epiglottic dysfunction due to isocyanate inhalation exposure and review the literature concerning this subject. Following inhalation exposure to diphenylmethane diisocyanate, our patient developed persistent repeated airway obstruction during inspiration. Fiberoptic rhinolaryngoscopy showed that the epiglottis obstructed the glottic airway during each inspiratory cycle. The epiglottic dysfunction was also well demonstrated by barium contrast cineradiography. Total epiglottectomy resulted in resolution of the patient's upper airway obstructive symptoms. Histologically, marked inflammatory changes of the epiglottis were noted, including a focal infiltrative pattern, focal fibrosis, edema, and reactive changes.

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Epiglottic dysfunction due to environmental exposure is a well-described entity. The most common causes of epiglottic dysfunction include trauma (thermal, chemical, and blunt), infection, allergy, neoplasm, and neurologic disorders. Due to the strategic location of the epiglottis at the junction of the airway and the digestive tracts, epiglottic dysfunction is an important and potentially life-threatening problem.

REPORT OF A CASE

A 34-year-old previously healthy man was admitted to another hospital with symptoms of dull, nonradiating left precordial chest discomfort, left upper quandrant pain, nasal congestion, fever, nausea, and vomiting that had started the day before presentation. He was a nonsmoker and denied any history of respiratory illness, asthma, allergic rhinitis, or other atopy. Physical examination, on initial presentation, revealed a diaphoretic man with a temperature of 39°C orally and normal findings on lung and cardiac examinations. Admission laboratory studies, including electrocardiography, chest roentgenography, complete blood cell count, chemistry survey profile, and urinalysis, disclosed no abnormalities. The discharge diagnosis after treatment with ampicillin sodium and supportive care was noncardiac chest pain probably secondary to pleuritis following a viral illness. The patient was followed up on an outpatient basis and treated for his chronic pleuritic chest pain and shortness of breath with indomethacin before being referred to the Pulmonary Medicine Clinic at our hospital. On evaluation by the Pulmonary Medicine Department 4 months after his initial admission, he continued to have chronic dry cough, shortness of breath on exertion, intermittent chest tightness, and pleuritic chest pain. During this pulmonary evaluation, it was discovered that he had begun working with an isocyanate compound 1 week before his original admission to the other hospital. His job involved making award plaques with a polyurethane coating resin containing 65% diphenylmethane diisocyanate and 35% aromatic hydrocarbons. He also complained of an unusual "clicking" sound on inspiration, associated with partial airway blockage that had been present since 1 month after his original exposure. He was noted to have wheezing at that time and was treated

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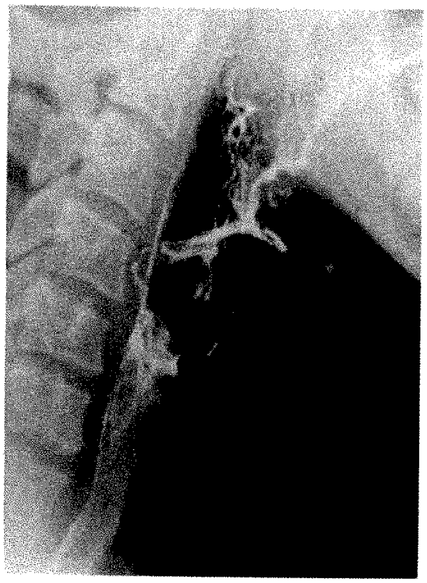

Fig 1.—Barium contrast cineradiograph indicating epiglottic closure of glottis during inspiration.

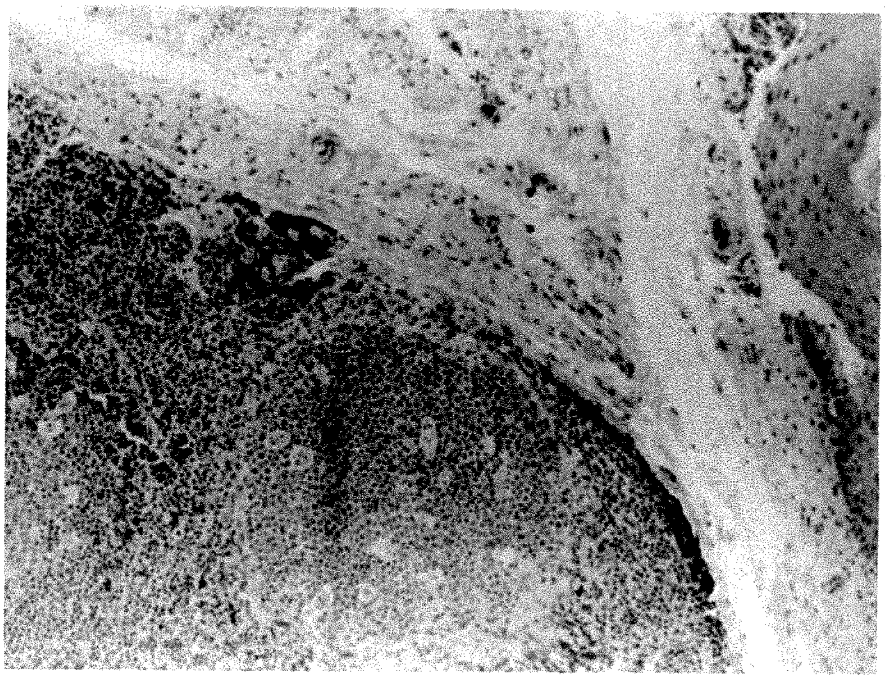

Fig 2.—Epiglottectomy specimen demonstrating reactive lymphoid hyperplasia (hematoxylin-eosin, original magnification ×40).

with bronchodilators. A diagnosis of isocyanate-induced asthma was made. The patient continued to have upper airway clicking with inspiration and was referred to the Otolaryngology-Head and Neck Surgery Clinic for evaluation. Examination with the flexible fiberoptic rhinolaryngoscope, 5 months after the initial exposure, revealed an epiglottis with redundant margins and a rather rigid character from superior to inferior. It moved posteriorly and inferiorly and would obstruct the laryngeal inlet with each inspiration. The epiglottic dysfunction was also well demonstrated by barium contrast cineradiography (Fig 1). This demonstrated that the epiglottis would "flop" posteriorly with each inspiration so that the tip was adjacent to the posterior pharyngeal wall. A similar motion was noted with swallowing. A total epiglottectomy was performed 6 months after exposure using direct microlaryngoscopy and microdissection instruments in conjunction with the carbon dioxide laser. A forceps was used to hold the tip of the epiglottis posteriorly as the carbon dioxide laser was used to remove the epiglottis at its base. Histologically, marked inflammatory changes of the epiglottis were noted, including marked lymphoid hyperplasia with multiple follicular reaction (Fig 2). The patient recovered from the epiglottectomy uneventfully, and this resulted in resolution of the his upper airway obstructive symptoms. Barium contrast cineradiography, performed 3 months postoperatively, confirmed the resolution of the intermittent airway obstruction and did not reveal episodes of aspiration. The patient's pulmonary symptoms have persisted.

COMMENT

Isocyanates are phosgenated primary amines with active NCO groups: monocyanates have one NCO group; diisocyanates, two; and polyisocyanates, three or more. Polyurethane products are polymers resulting from the combination of chemicals containing two highly reactive isocyanate groups with a polyol in a polymerization reaction. Today there are a wide range of products that contain polyurethanes. Examples include paints, lacquers, varnishes, shoe soles, furniture, models, pillows, and packaging materials.[1]

The first clinical report of health-related problems associated with isocyanate exposure was published in 1951.[2] Since that time, several reports have documentated that prolonged exposure to isocyanates can lead to serious long-term problems.[3-8]

Reactions to isocyanates are usually categorized as toxic or asthmatic. The toxic effects are associated with higher concentrations or more prolonged exposure. It has been noted that the toxic reactions usually require a concentration of greater than 0.5 ppm and influence nearly all individuals exposed.[3] The exposure is often the result of an accident or poor safety precautions resulting in a high degree of contact. The injuries frequently include pulmonary, ocular, and dermatologic abnormalities.

The asthmatic effects are heralded by eye, nasal, and pharyngeal irritation. This may be followed by chest tightness, wheezing, and dyspnea shortly after exposure. Symptoms are usually associated with headaches, nausea, and vomiting if the exposure was significant. Coughing and wheezing are often worse in the evening, after leaving work, and this may lead to failure of the patient or the medical practitioner to relate the problem to the work environment.[1]

Initial examination may reveal wheezes or rhonchi with various ranges of intensity. Chest roentgenograms are commonly normal or show mild, patchy infiltrates and increased lung markings. The initial diagnosis is frequently bronchitis, broncheolitis, pneumonitis, or asthma.[4]

Some of the exposed individuals appear to become sensitized since they suffer asthmatic-type reactions on reexposure, even to extremely low concentrations.[1] Although the decrease in ventilatory capacity noted during these exposures is usually short-lived, long-term changes in ventilatory capacity have been reported.[3]

Nonrespiratory health effects mainly include skin sensitization and direct irritative skin and mucous membrane reactions. Direct contact with the eye causes severe irritation of the conjunctiva and cornea, which can lead to permanent damage. There has been no evidence, to date, that isocyanates cause neurologic sequelae or that they are carcinogenic.[1]

Our literature review failed to reveal a previous report of epiglottic dysfunction. This dysfunction may be the result of either direct irritation or a true sensitization such as noted with the asthmatic reactions. Histologic examination revealed chronic inflammatory infiltrates in the submucosal areas, as well as focal fibrosis in the mucosa and submucosa. This picture, combined with the decrease in flexibility of the epiglottis noted on examination and contrast cineradiography, suggests a severe and apparently irreversible change in the epiglottis. It appeared that the movement of the stiffened epiglottis was at the mercy of the airstream and movement of secretions as it flopped back and forth on the petiole. The patient experienced frequent episodes of severe coughing paroxysms (with and without eating and drinking), which were consistent with minor episodes of aspiration. This would suggest that the epiglottis no longer efficiently served its protective function for the glottis.

Diagnosis of isocyanate sensitivity remains a problem, since there is no definitive test available. The best available method of testing for reactivity to isocyanates is an inhalation challenge test. This is somewhat risky and should be performed only at specialized centers. It involves exposure to increasing concentrations of isocyanates on successive days, while lung function is monitored throughout the rest of the day and night.[9] This should not be performed unless the results of the test wil significantly improve the management of the patient.

Some authors have attempted to demonstrate specific IgE antibodies to isocyanates, but, to our knowledge, no commercially available indicator of this association exists. It has been demonstrated that there is no association between sensitivity to isocyanates and total IgE level.[10]

The main treatment for the asthmatic-type reactions remains prevention. Provision must be made for effective removal of isocyanates from the breathing environment of exposed workers. First aid measures after exposure should include immediate removal from the contaminated area and application of supplemental oxygen to dyspneic victims. Hospitalization may be necessary. There is no satisfactory treatment presently available for isocyanate-related asthma.

Prophylactic measures available to avoid bronchoconstriction after inhalation exposure include the use of cromolyn sodium prior to the work shift or administration of theophylline or β-adrenergic agonists.[5] These measures did not appear to affect the epiglottic dysfunction portion of our patient's condition.

CONCLUSIONS

Pulmonary dysfunction after isocyanate exposure is a well-documented entity. Adequate steps should be taken to avoid prolonged exposure to these substances. We have reported a case of epiglottic dysfunction that began after inhalational exposure to isocyanates and accompanied isocyanate-induced asthma. Total epiglottectomy resulted in satisfactory resolution of the patient's upper airway dysfunction and recurrent aspiration episodes. The epiglottectomy appeared to have no effect on his asthmalike symptoms.

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Melkersson-Rosenthal Syndrome

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• **Melkersson-Rosenthal syndrome is a rare condition, classically associated with a triad of facial and/or lip edema, fissured tongue, and relapsing facial palsy. This article offers a review of the literature and presents two cases of Melkersson-Rosenthal syndrome associated with elevated serum levels of angiotensin converting enzyme in two patients of Thai descent.**

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Melkersson-Rosenthal syndrome (MRS) is a distinct and rare otolaryngologic disorder occurring frequently between the second and fourth decades of life, with primary manifestations of relapsing unilateral facial paralysis, fissured dorsum of the tongue (lingua plicata), and unilateral edema of the face and/or lips.[1] The male-female ratio is 1.1:1 with no predilection to race.[2-5] The incidence of the syndrome in Europe was found to be 1 in 2100.[6]

The most dominant feature of MRS is recurrent, painless, nonpitting edema of regions of the face.[2-4,7-11] The onset of edema is usually sudden and may assume a reddish-brown appearance. In most cases, it occurs prior to facial paralysis.[1,2,7,8,11] According to New and Kirch,[12] the tissues involved in order of frequency are those of the upper lip, cheek, lower lip, nose, eyelids, and alveolar process. Other areas of involvement can include the buccal mucosa, glottis, palate, sublingual mucosa, gingiva, tongue, hands, chest, and buttocks.[1,3,5,9,13] The edema tends to occur at irregular intervals, ranging from weeks to years, and with subsequent attacks, may become permanent.[1-3,7,11,14]

Idiopathic lower motoneuron facial paralysis is virtually indistinguishable from Bell's palsy. The paralysis is usually recurrent and may be unilateral or bilateral with involvement of all or part of the facial nerve.[2,4,8,15,16] The literature reveals involvement of the facial nerve in 30% to 90% of documented cases of MRS.[2,4,7,9,10,16] The seventh nerve palsy tends to present in conjunction with facial edema, usually with spontaneous recovery, but residual facial paresis can occur.[2,4,8,11,16-18] In addition, other cranial nerve involvement may occur, including the oculomotor, optic, auditory, olfactory, glossopharyngeal, hypoglossal, and trigeminal nerves.[4,7,9,19]

Completion of the classic triad includes lingua plicata, a deep-fissured tongue. It is the least consistent finding of the triad, found in 30% to 77% of patients with MRS, while occurring in only 0.5% to 5% of the general population.[4,8,9] The lingua plicata associated with MRS is usually present at birth and is commonly an incidental finding.

Melkersson-Rosenthal syndrome is also associated with other clinical entities, including migraine-type headaches, trigeminal neuralgias, otosclerosis, craniopharyngioma, congenital megacolon, syphilis, herpetic eruptions, osteoporosis, malignant lymphogranulomatosis, leukemia, premenstrual tension, and psychotic disorders.[2-4,7-11,13,15,19-22] In addition, constitutional symptoms such as concomitant elevation of body temperature, chills, and salivary and lacrimal gland secretory disturbances may be present.[2,3,11,23]

Klaus and Brunsting[24] have described the occurrence of this syndrome in an incomplete or oligosymptomatic form in which only two of the principal manifestations are present. In the last 10 years, the literature has revealed cases of oligosymptomatic MRS in which only one of the principal manifestations of the triad was present.[3,4,5,25] The most frequent oligosymptomatic form was found to be Meischer's granulomatous cheilitis. Diagnosis was confirmed in all cases by biopsy of the edematous region with the classic pathologic findings of perivascular and paravascular aggregations of lymphocytes, plasma cells, and histiocytes and the presence of noncaseating epithelioid cell granulomas with multinucleated giant cells in an edematous connective tissue.

REPORT OF CASES

Case 1.—A 54-year-old Oriental woman, first generation Thai descent, presented to Wilford Hall US Air Force Medical Center, Lackland Air Force Base, Tex, with recurrent incomplete right facial paralysis, right facial and lip swelling, and unilateral right frontotemporal headaches. These episodes originally occurred when the patient was approximately 30 years of age, with recurrent facial paralysis occurring approximately every 1 to 3 years. Right facial and lip edema originally preceded the onset of the facial paralysis but, after recurrent episodes, had become persistent. The patient's medical history was significant only for insulin-dependent diabetes mellitus of 10 years' duration. Physical examination revealed distinct asymmetric swelling of the right side of the face, eyelids, and upper lip; incomplete right seventh nerve paralysis with sparing of the marginal branch; and a deep-fissured dorsum of the tongue. The findings of cortical audiometry, Schirmer's test, computed tomography of the temporal bones, and roentgenography of the chest were normal. Laboratory data included an elevated erythrocyte sedimentation rate of 35 mm/h (normal, 0 to 30 mm/h) and a serum angiotensin converting enzyme level of 34 U/L (normal, 10 to 30 U/L). Results of the remainder of the laboratory studies, including the serum calcium level, were within normal limits.

The patient was observed initially on a daily basis without treatment, and 6 weeks after initial presentation, complete recovery of right seventh nerve function was noted. Convalescent serum assay 3 months after initial presentation revealed that the

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angiotensin converting enzyme level was normal (18 U/L).

Case 2.—A 13-year-old Oriental boy, second generation Thai descent, presented to Wilford Hall US Air Force Medical Center with the third episode of incomplete unilateral facial paralysis associated with facial and lip edema. His parents stated that this was the third episode over a 5-year period, occurring twice on the left side of the face and once on the right. The patient had no significant medical history. Physical examination revealed an incomplete left-sided seventh nerve paralysis of all branches, obvious left facial and lip edema, and lingua plicata. An audiogram revealed an absent left stapedial reflex and rollover on the left. Results of the Schirmer test, cortical audiometry, computed tomography of the temporal bones, and roentgenography of the chest were all within normal limits. Laboratory studies revealed an elevated serum angiotensin converting enzyme level of 138 U/L (normal, 8 to 52 U/L). Results of the remainder of the laboratory studies, including the erythrocyte sedimentation rate and the serum calcium level, were within normal limits.

This patient was initially observed as an outpatient on a daily basis, and a therapeutic regimen of oral prednisone (150 mg/d for 10 days) was begun. Complete recovery of seventh nerve function was observed 4 weeks after presentation. Convalescent assay of angiotensin converting enzyme 3 months later revealed that the level was 42 U/L (normal, 8 to 52 U/L).

COMMENT

The exact cause of MRS remains unknown. Theories identify infectious (bacterial or viral), neurotropic, allergic/immunologic, and genetic processes as possible causes.[2,4,8-11,19,26-28] The syndrome's uncertain pathogenesis, coupled with its rarity and oligosymptomatic forms, makes its diagnosis difficult. Clinical presentation, along with the aid of pathologic assessment, is, to date, the only means of obtaining a diagnosis. Presented herein are two cases of this syndrome, both with the classic clinical triad of MRS. Laboratory assays revealed that the serum angiotensin converting enzyme level was elevated in both cases.

In addition to a complete history and physical examination, topognostic studies of seventh nerve function should be obtained as indicated, along with a computed tomographic scan of the temporal bones. Further studies should be tailored to the individual patient's clinical presentations. Laboratory evaluation should include an acute and convalescent assay of angiotensin converting enzyme. The angiotensin converting enzyme level has been documented to be elevated in several types of pulmonary disease, including chronic bronchitis, emphysema, carcinoma of the bronchus, bronchial asthma, and cystic fibrosis. Elevation of the angiotensin converting enzyme level has also been documented in sarcoidosis, severe diabetic retinopathy, Gaucher's disease, and granulomatous conditions, including Hodgkin's disease, biliary cirrhosis, tuberculosis, and MRS.[15,29,30] Angiotensin converting enzyme levels have been documented to parallel clinical changes in sarcoidosis and MRS.[15,29]

This syndrome is usually self-limited, with relapsing seventh nerve paralysis and facial and/or lip edema.[2,4,8,9,11,16] However, after repeated episodes of this disorder, the facial and/or lip edema can become chronic and may be replaced by fibrous tissue. Treatment of MRS should be aimed at the facial paralysis and associated edema.[2-4,7-9,11,16-18]

In both of our patients, the angiotensin converting enzyme level returned to normal during convalescence. Only recently has a correlation been established between serum levels of angiotensin converting enzyme and MRS.[15] We hope that in the future, the use of this laboratory assay will aid in the diagnosis of this rare disorder.

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Percutaneous Endoscopic Gastrostomy as a Standard Procedure in Head and Neck Surgery

Jan A. Roukema, MD, PhD; Christiaan van der Werken, MD, PhD; Job R. Juttmann, MD, PhD

• Adequate nutritional support is essential in patients with head and neck cancer, especially if extended oropharyngeal surgery is indicated. Enteral nutrition is an effective and safe alternative to parenteral nutrition, but the use of nasogastric tubes has several disadvantages in these patients. We describe our experience with percutaneous endoscopic gastrostomy as a standard procedure prior to surgical resection in patients with head and neck cancer.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:730-731)

Patients with malignant neoplasms of the oral cavity and oropharynx present special nutritional problems because they often have a history of excessive smoking, dietary indiscretions, and alcohol abuse. Malnutrition may be compounded by the anatomic location of the cancer resulting in obstruction or pain on deglutition. Adequate nutritional repletion is of utmost importance in these patients before and after surgery. Enteral nutrition via feeding tubes is a very effective, inexpensive, and safe alternative to total parenteral nutrition. Nasogastric tubes, however, are unsatisfactory because they often cause nasopharyngeal ulcerations and gastroesophageal reflux, complications that should be avoided, especially in patients recovering from extended and reconstructive oropharyngeal surgery.[1]

We describe our experience with percutaneous endoscopic gastrostomy (PEG) as a standard procedure prior to surgical resection of oropharyngeal cancer. Percutaneous endoscopic gastrostomy is a well-accepted procedure that allows enteral nutritional support in patients who are unable to swallow after cerebral trauma or extended head and neck cancer.[2] In the second group of patients, this procedure is occasionally used during radiotherapy or to relieve patients with poor chances of survival.[3,4] Our extensive experience with a low complication rate of PEG in patients with neurologic disorders convinced us to use PEG as a standard procedure in patients with oropharyngeal malignancy prior to resection of their cancer.[5]

PATIENTS AND METHODS

Between 1986 and 1988 we performed PEG in 100 patients for various reasons (Table). In patients with severe neurologic impairment, multiple trauma, or respiratory failure, a tracheostomy was usually performed in combination. In 10 consecutive patients selected for extensive oropharyngeal cancer surgery, PEG was performed under general anesthesia as the first step of the surgical procedure.

Seven patients had carcinoma of the tongue with regional extension and three patients had carcinoma of the floor of the mouth. Various techniques of PEG have been described.[2] We initially used the introducer technique, fixing the stomach to the abdominal wall only by a Foley catheter. Because intra-abdominal leakage occurred in two patients because of a deflated balloon, we decided to add another gastropexia: after introduction of the gastroscope, the appropriate side for gastrostomy was indicated by diaphanoscopy. Under endoscopic control, the stomach first was fixed to the abdominal wall by Dennison strings (Figs 1 and 2).[6] Three of these strings were placed in a triangle shape and fixed with a fisherman's lead (Fig 2, C). In the center of this triangle a guide wire was

Indications for Gastrostomy

	No. of Patients
Neurologic impairment	30
Multiple trauma	26
Gastrointestinal surgery	14
Gastrointestinal obstruction	12
Head and neck surgery	10
Respiratory failure	8
Total	**100**

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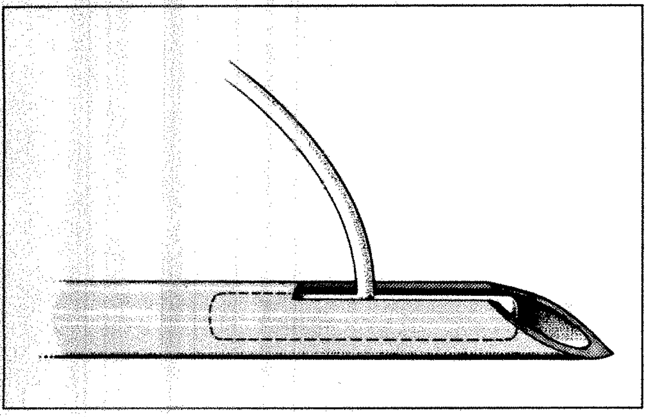

Fig 1.—Close-up view of needle with Dennison string.

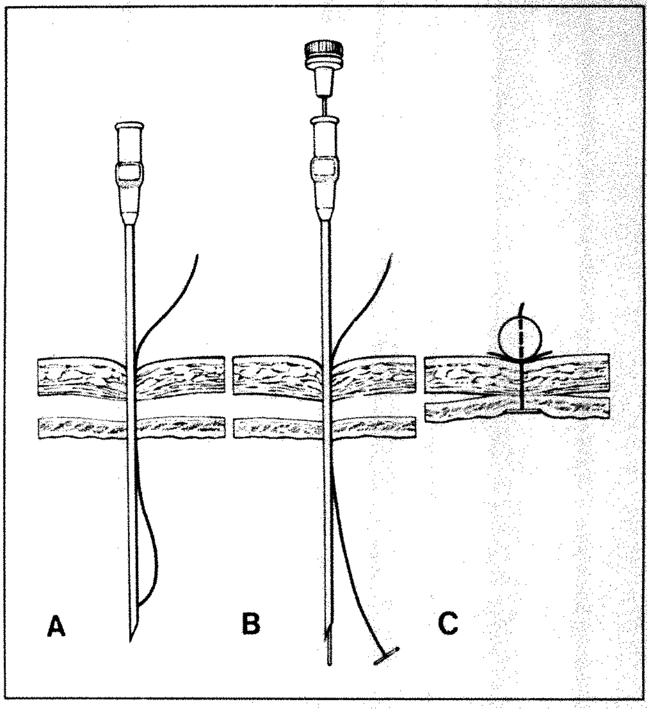

Fig 2.—Fixation technique.

introduced through a needle. Using this guide wire, a trocar with a peel-away sheath was inserted and the trocar removed after the plastic sheath had entered the gastric lumen. Through this sheath, a 14F silicon Foley catheter was inserted. When the balloon was filled with water, the sheath was removed and the catheter fixed to the abdominal wall under slight traction. This procedure usually took no more than 15 minutes. After gastrostomy, surgical treatment of the oropharyngeal cancer was performed.

Enteral feeding was started the first day after surgery.

RESULTS

In the first 23 patients, gastrostomy was performed without additional fixation by Dennison strings. Two of these patients had intraperitoneal leakage because of a deflated catheter balloon. Laparotomy was necessary in both patients. In all 10 patients with head and neck cancer, the described technique combining gastrostomy with gastropexy using Dennison strings was applied. The T-fasteners were simply cut about 6 weeks after gastropexy and the tube was removed at the same time if normal food intake was possible. In 4 patients the PEG tube feeding was continued for some weeks during postoperative radiotherapy. In 1 patient with a large cancer of the floor of the mouth there were long-lasting postoperative complications due to partial necrosis of the myocutaneous pectoralis major flap. This woman was discharged from the hospital 4 weeks after surgery; she managed PEG tube feeding herself at home for 8 more weeks.

COMMENT

Feeding by the enteral route provides a safe, simple, and economical alternative to total parenteral nutrition. Nasogastric feeding, however, has general disadvantages in patients after extended oropharyngeal surgery: the tube may cause intolerable discomfort with wound healing disturbances, reflux esophagitis, and local mucositis. The ease of placement and lack of complications have made PEG with gastropexy a useful alternative. Our experience with this procedure in a group of 100 patients confirms data from the literature.[2,3,5,7]

We recently started to use this technique as a standard procedure in patients with head and neck cancer scheduled for surgery with or without postoperative radiotherapy.

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Pachyonychia Congenita

Manifestations for the Otolaryngologist

Sheldon P. Hersh, MD

• When discovered, leukoplakia of the oral cavity is commonly an acquired lesion. Pachyonychia congenita is a member of a rare group of disorders in which congenital white lesions of the oral cavity are present. Additional findings of note to the otolaryngologist are described as well.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:732-734)

White lesions of the oral cavity are, for the most part, acquired byproducts of the multitude of events occurring daily in the oral cavity. Less commonly, they may appear as manifestations of either local or systemic diseases such as lupus erythematosus and others. Rarely encountered is a group of congenital white lesions of the oral cavity herein referred to as oral genodermatoses. One of these disorders, pachyonychia congenita (PC), is presented along with some of its potential otolaryngologic-head and neck manifestations.

Pachyonychia congenita was first described by Jadassohn and Lewandowsky[1] in 1906 as an anomaly in which dystrophic fingernails and toenails occurred together with specific cutaneous and mucus membrane changes that may first be noted at birth or in early childhood.

The remarkable fingernails (Fig 1) in these patients are the sine qua non of this disorder. Steiglitz and Centerwall[2] have found that approximately 97% of cases reviewed have dystrophic nails with all fingernails and toenails being affected. Together with marked thickness, these nails take on a yellow-brown discoloration with pinched margins and an upward angulation of the distal tips.[3] These hyperkeratotic nails can lead to difficulties in digital dexterity, and cosmesis remains a lingering concern.

Cutaneous findings oftentimes reveal plantar and palmar hyperkeratosis in conjunction with hyperhidrosis.[4,5] Follicular keratosis of the extensor surfaces of the knees and elbows may be present. They are usually of the acneiform type.[3,5] These keratotic lesions may at times appear on the buttocks and lumbar regions as well.[6] Plantar bullae[3] secondary to hyperkeratosis and hyperhidrosis may become infected and lead to additional difficulties.

Gorlin and Chaudhry[3] described the oral lesions as white, opaque thickenings of discrete or confluent areas of the oral cavity. The entire buccal mucosa may at times be involved. An associated overgrowth of *Candida albicans* has been noted with some of these leukoplakic lesions.[4] Angular cheilosis has been described as well.[3] The tongue may often appear with scalloped edges (Fig 2), and may be partially or totally covered by a leukoplakic blanket. Aphthous ulcerations of the oral cavity have been noted to occur with PC,[5] and neonatal teeth have been described in a number of affected individuals.[2,6,7]

A number of other affected sites that occur with less frequency include the larynx, eyes, teeth, hair, and ears. The likelihood of one of these less commonly affected sites being involved will depend, for the most part, on the pedigrees under study. A rare presentation in one pedigree may stand out as a common finding in another. Gorlin and Chaudhry[3] noted the existence of white plaquelike lesions involving the interarytenoid area of the larynx. Cohn et al,[8] in a recent article, described multiple white lesions involving the ventricles, true cords, and subglottic areas of the larynx. Steiglitz and Centerwall[2] presented a pedigree in which laryngeal involvement was a common presentation. Some members of this pedigree had experienced laryngeal obstruction that ultimately necessitated tracheostomy. Dystrophic changes in the hair and cornea were described by Witkop and Gorlin,[9] Forslind et al,[4] and Steiglitz and Centerwall.[2] In addition, Forslind et al[4] made note of the possible presence

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of thickened tympanic membranes with a resultant conductive hearing loss.

Pachyonychia congenita has been divided into various types based on clinical presentation. Kummer and Loos[10] proposed the following division: type 1, symmetrical keratosis of the hands and feet along with follicular keratosis of the body; type 2, oral leukoplakia in addition to those findings in type 1 (most common); and type 3, corneal dyskeratosis plus types 1 and 2 clinical findings.

Additional subdivisions have been proposed in the literature but may, in fact, be artificial in nature as the subdivisions may represent possible variations in phenotypic expression of a single disease entity.

REPORT OF A CASE

This 45-year-old man was seen in consultation for a totally unrelated problem. On routine otolaryngologic examination, a rather remarkable-appearing tongue was noted (Fig 2), which obviously led to further questioning. His fingernails were remarkable as well (Fig 1). He was aware that he had some form of genetic illness as his son had similar findings. To the best of his knowledge, no other family members were affected. Permission to obtain a biopsy specimen from the tongue and to obtain additional investigations was refused.

Pathologic Findings

There do not appear to be any microscopic features that are strictly pathognomonic of PC. A number of the genodermatoses may have histologic features that are indistinguishable from those found in PC.[9] Steiglitz and Centerwall[2] have found that all three germ layers may be involved: the ectoderm, nails, skin, hair, teeth, and oral mucosa; the endoderm, larynx; and the mesoderm, joints and laryngeal cartilage. It was thus concluded that the histologic picture of the disparate sites was essentially similar.

Witkop and Gorlin[9] performed exfoliative cytologic analyses of the oral mucosa and tongue. They noted that the epithelium was acanthotic with uniform intracellular vacuolization. Additionally, the intercellular bridges were not present in the prickle cell layer. A marked parakeratosis was in evidence, while the stratum granulosum was lacking. Gorlin and Chaudhry[3] obtained representative biopsy specimens of the tongue and oral mucosa with findings similar to those obtained by Witkop and Gorlin.[9] Cohn et al[8] found the ultrastruc-

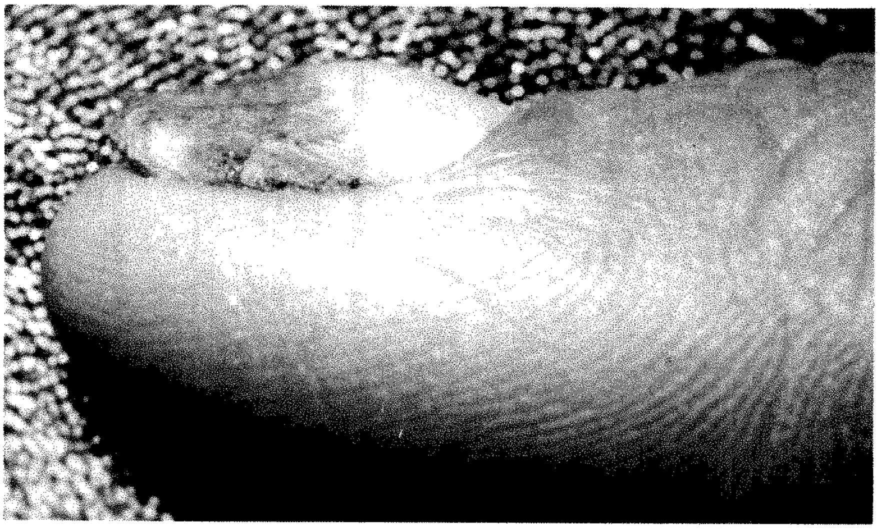

Fig 1.—Hypertrophic fingernail with characteristic upward angulation of distal tip.

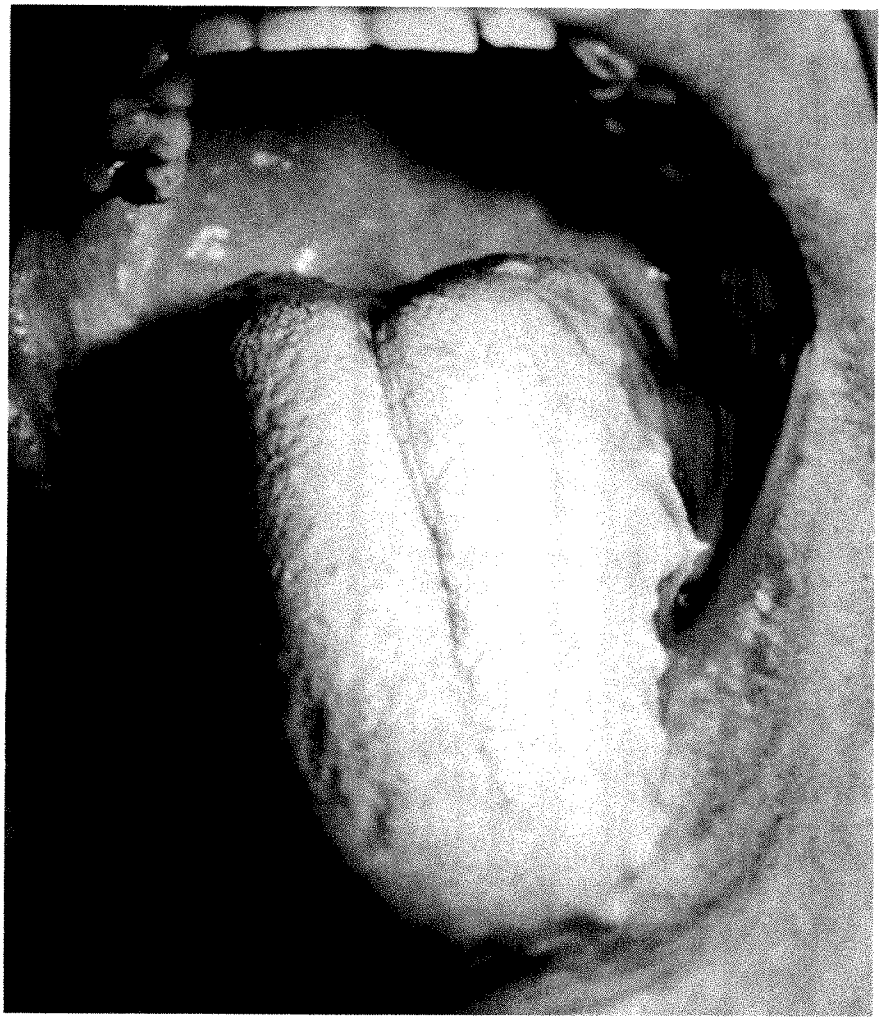

Fig 2.—Near total leukoplakic covering of tongue along with scalloped perimeter.

ture of laryngeal lesions to be identical to those found in the above studies. Nail pathology[4,11,12] seemed to be confined to the nail bed. An abnormal granular layer produces increased amounts of keratin, which, along with a deficient nail bed adhesion, gives rise to a thickened elevated nail.[12]

Electron-microscopic studies of PC[13] have revealed an increase in the tonofibrils of the basal cells. This increase in tonofibril density was more evident in the stratum spinosum, while intracellular edema was present in both the stratum spinosum and the granular layer.

Genetics

Pachyonychia congenita is transmitted as an autosomal dominant with high penetrance and variable phenotypic expressivity.[2,13,14] Isolated cases of what appears to be an autosomal recessive transmission have been reported.[15,16] A significant history of consanguinity has been revealed in these recessive cases.

COMMENT

As otolarynologists, we are accustomed to seeing various forms of leukoplakia in the oral cavity. In most cases, one can associate these white lesions with some form of local or systemic cause. A rare group of genodermatoses has been described and can, for the most part, be easily diagnosed if the appropriate history is available. No specific laboratory tests or definitive pathologic criteria are present to definitively validate the diagnosis. Treatment is essentially symptomatic, with the major emphasis placed on ameliorating the discomfort, both physical and psychological, of the hyperkeratotic skin and nail lesions. As the pathologic findings have indicated, and the literature has verified, the leukoplakic lesions of the oral cavity do not undergo malignant transformation.

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In Other AMA Journals

AJDC

Management of Coin Ingestion
Paul R. Joseph, MD, PC; Jeff E. Schunk, MD; Howard Corneli, MD; Robert Bolte, MD (*AJDC.* 1990;144:449)

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Donald L. Foster, MD, FAAP; E. Martin Caravati, MD, FACEP; Newell E. McElwee, PharmD (*AJDC.* 1990;144:449)

β-Hemolytic Non-Group A Streptococci and Pharyngitis
Hevio Cimolai, MD, FRCPS; Gregory F. Hayden, MD; J. Owen Hendley, MD (*AJDC.* 1990;144:449)

***P* Values**
George W. Brown, MD (*AJDC.* 1990;144:493-495)

Nonpigmented Papillary Carcinoma in a Black Thyroid Gland

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• **A case of papillary thyroid carcinoma occurring in a 27-year-old man with black thyroid syndrome is reported. The tumor, in contrast to the remaining thyroid, was not pigmented. The significance and potential utility of the differential pigmentation are discussed.**

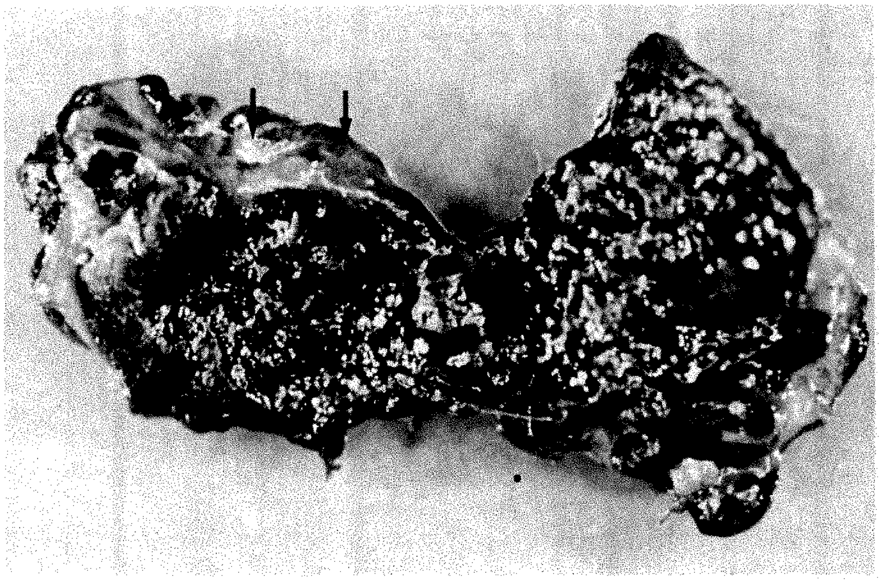
***(Arch Otolaryngol Head Neck Surg.* 1990;116:735-737)**

Intense black gross pigmentation of the thyroid gland and its association with minocycline hydrochloride administration are well described in the pathology literature.[1-4] Black discoloration of thyroid epithelium was originally described in rats that received minocycline for a period of several weeks.[5] This "melanosis" is an entirely benign process: no evidence of significant pathologic consequence has been demonstrated. We report a case of black thyroid occurring in a 27-year-old man, emphasizing the benign nature of this condition and noting the absence of black thyroid pigment within a coincidental papillary thyroid carcinoma.

REPORT OF A CASE

A 27-year-old white man was referred to the Ohio State University Hospital, Columbus, for follow-up of metastatic thyroid carcinoma. The patient had noted a firm, mobile mass in the right side of his neck in June 1987. Biopsy of the mass, which was 2 cm in diameter, was performed in September 1987. The biopsy revealed lymph node metastasis of a papillary thyroid carcinoma. The patient was in good health, and findings of the general physical examination were unremarkable. At follow-up, a 4-cm healed linear incisional scar was present in the right lateral aspect of the neck, several centimeters above the clavicle. The thyroid gland was symmetric and without discrete palpable nodules. An ill-defined "fullness" was noted, however, in the superior aspect of the right lobe. No neurologic deficit or other evidence of extension of disease was demonstrable. Laboratory studies revealed that the serum electrolyte levels and the differential blood cell count were normal, as were results of thyroid function tests (thyroxine, 129 nmol/L [normal range, 58 to 148 nmol/L]; triiodothyronine uptake, 0.38 [normal range, 0.30 to 0.40]; and thyrotropin, 1 mU/L [normal range, 0 to 7 mU/L]). Thyroid scan was remarkable for a small defect in the upper pole of the right lobe. The patient underwent a total thyroidectomy in December 1987. The specimen was a 3.5 × 2.0 × 1.1-cm uniformly black thyroid gland (Fig 1) with a normal texture and contour except for a 0.7-cm, firm, light-brown nodule within the superior pole of the right lobe. Histopathologic examination of the nodule revealed a proliferation of atypical cells forming papillae and, in

Fig 1.—The thyroid gland is symmetric and free of gross lesions. The tumor, itself, was being sectioned as this gross photograph was taken. The brown capsule (arrows), normally indistinct from the similarly colored thyroid gland, in this case stands out clearly in contrast to the black thyroid tissue.



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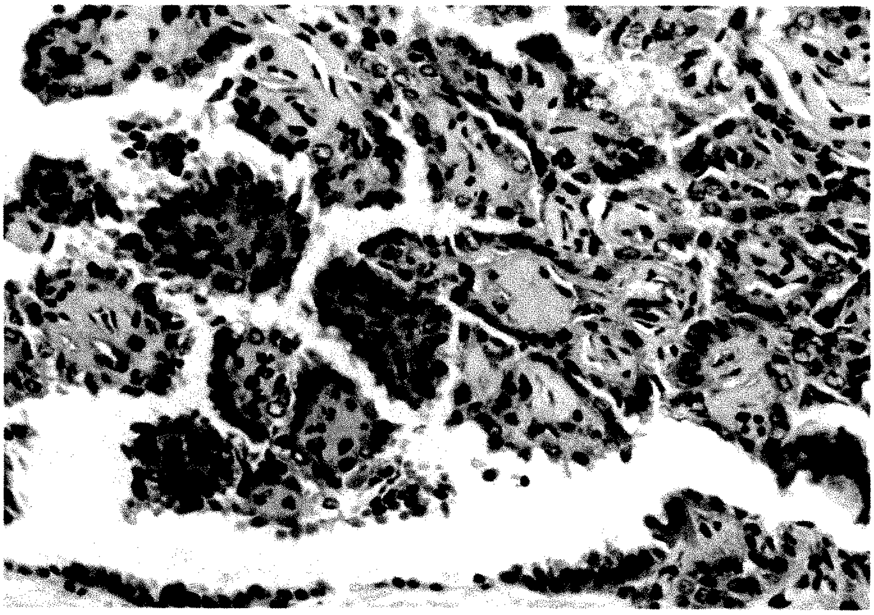

Fig 2.—The tumor was composed primarily of papillary structures containing cytologically abnormal cells (hematoxylin-eosin, original magnification ×40).

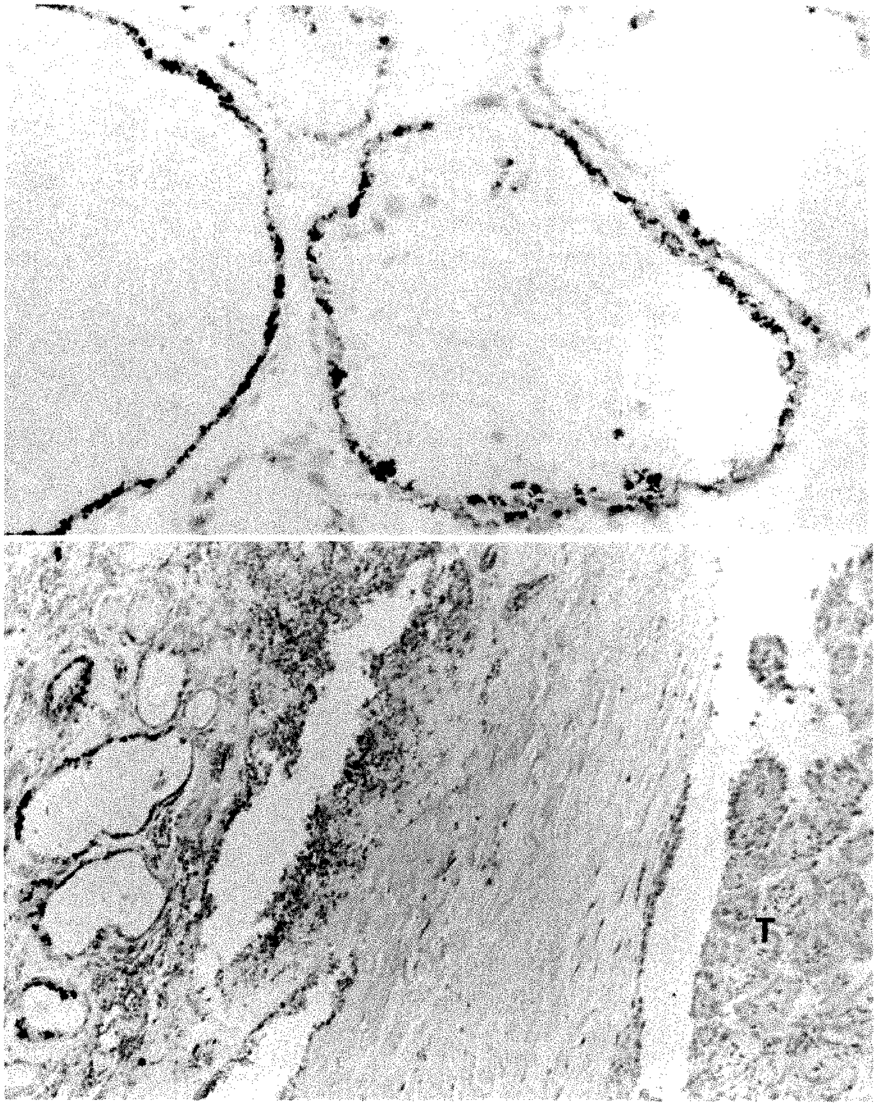

Fig 3.—The non-neoplastic thyroid tissue exhibited large amounts of Fontana-positive pigment (top) in contrast to the tumor (T), which was devoid of pigment (bottom) (Fontana's stain, original magnification ×40 [top] and ×16 [bottom]).

some areas, follicular structures with cytologic and architectural features diagnostic of papillary carcinoma (Fig 2). The remainder of the thyroid gland was histologically normal except for prominent, black, granular pigment in the cytoplasm of the thyroid epithelial cells, within macrophages located in the interstitium, and in the colloid substance. The neoplastic cells contained no demonstrable pigment (Fig 3).

COMMENT

This case represents another example of black thyroid syndrome, which has been associated with minocycline administration in all but two of the reported cases.[1,2] Further investigation of the patient in this case revealed a history of minocycline hydrochloride therapy for acne vulgaris: 100 mg twice a day from June 1980 to November 1982. Recent studies have demonstrated that the minocycline-associated black thyroid pigment has the color and chromatographic properties of minocycline oxidation products.[6] In addition, other substances may also produce the black pigment, as in the Gunn rat and, perhaps, in two cases of "idiopathic black thyroid." The staining properties of black thyroid pigment are those of melanin, although there is coincidental accumulation of lipofuscin in epithelial cells of black thyroid glands.[1] The pigment in this case exhibited histochemical staining properties identical to those described in the literature: Fontana stain positive, labile to melanin bleach, and iron stain negative.

One point of clinical relevance is that this condition of black thyroid pigmentation, be it a syndrome of drug-related, "idiopathic," or other causation, is an entirely benign process. Although encountering an unanticipated case of striking thyroid melanosis may be disconcerting, the black pigment is a benign anatomical curiosity and in and of itself does not indicate need for thyroidectomy.

Of particular interest in this case was the complete absence of black pigment in the neoplastic thyroid cells of both the primary papillary carcinoma and the lymph node metastasis. The striking contrast between nonpigmented tumor cells and intensely pigmented non-neoplastic thyroid tissue suggests a basic functional divergence between neoplastic and non-neoplastic thyroid cells. Cellular metabolic rate may represent this "functional" difference, since minocycline pigmentation is accelerated by thyrotropin stimulation and retarded by thyroxine.[7] Of interest is the report by Wajda et al[8] of a follicular adenoma in a black thyroid gland that was intensely pigmented. This tumor was more heavily, or "preferentially," pigmented relative to the surrounding thyroid. The differential pigmentation may represent a functional difference between normal and neoplastic thyroid, which reliably (although inconsistently) differentiates tumor from surrounding gland. Such differential pigmentation may be useful in providing a grossly assessable topographic index of tumor or suspicious, "divergent" areas.

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In Other AMA Journals

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Mark A. Malangoni, MD; David H. Livingston, MD; Gerald Sonnenfeld, PhD; Hiram C. Polk, Jr, MD (*Arch Surg.* 1990;125:444-446)

Pancreaticoduodenectomy: University Experience and Resident Education
Ralph J. Doerr, MD; Ilhan Yildiz, MD; Lewis M. Flint, MD (*Arch Surg.* 1990;125:463-465)

Upper Airway Obstruction due to Tonsillar Lymphadenopathy in Human Immunodeficiency Virus Infection

Dennis H. Kraus, MD; Susan J. Rehm, MD; James P. Orlowski, MD; Raymond R. Tubbs, DO; Howard L. Levine, MD

• Head and neck manifestations of human immunodeficiency virus (HIV) infection are common and include diffuse cervical lymphadenopathy, cutaneous and mucosal Kaposi's sarcoma, mucosal herpes simplex infection, upper aerodigestive tract candidiasis, and parotid lymphadenopathy and cysts. Recurrent otitis media and chronic sinusitis have been noted in the pediatric HIV population. We describe a patient with HIV-associated tonsillar and adenoid lymphadenopathy and upper airway obstruction. Pathologic analysis of the tonsillar tissue revealed severe lymphofollicular hyperplasia similar to that of other lymphoid tissue in HIV infection. The importance of symptomatic treatment of the airway obstruction is stressed.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:738-740)

Patients with human immunodeficiency virus (HIV) infection develop an array of head and neck manifestations during the natural history of this disease. Generalized lymphadenopathy with cervical involvement is a common finding. However, involvement of the lymphoid tissue in Waldeyer's ring has rarely been documented. This report details the case of an adolescent patient with HIV-associated tonsillar and adenoid lymphadenopathy and symptomatic upper airway obstruction. Pathogenesis, differential diagnosis, and management are reviewed.

REPORT OF A CASE

A 17-year-old boy had received multiple blood transfusions between 1983 and 1985 during scoliosis surgery. When one of the blood donors was subsequently diagnosed with acquired immunodeficiency syndrome, the patient was tested and found to have HIV antibodies by both enzyme-linked immunosorbent assay and Western blot analysis.

On baseline examination in April 1987, he denied symptoms related to HIV infection. He had long-standing dyspnea on exertion related to severe thoracic deformities. There was diffuse lymphadenopathy and bilateral tonsillar enlargement. His HIV infection was classified as Centers for Disease Control[1] clinical group IV. His CD4 (T helper, T4) lymphocyte count was 185/mL (normal, 436 to 1394/mL).

Over the next 9 months the patient's respiratory symptoms progressed. He had dyspnea and cyanosis on mild exertion and used continuous oxygen supplementation every night. His tonsillar hypertrophy progressed, with the tonsils approximating in the midline, and his voice was hyponasal. Pulmonary function tests revealed a mixed obstructive and restrictive pattern.

At the time of otolaryngology consultation, the patient was in mild respiratory distress and required continuous oxygen therapy by nasal cannula. Physical examination revealed severe kyphoscoliosis, massive tonsillar and adenoid enlargement, and diffuse lymphadenopathy. There were no signs of active tonsil or adenoid infection. In July 1988, the patient underwent tonsillectomy and adenoidectomy. Postoperatively, a posterior nasal pack was necessary because of diffuse adenoid bed bleeding. The patient received prophylactic intravenous injections of vancomycin hydrochloride while the posterior nasal pack was in place. The patient remained intubated in the intensive care unit because of his respiratory condition until the pack was removed in the

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From the Departments of Otolaryngology and Communicative Disorders (Drs Kraus and Levine), Infectious Diseases (Dr Rehm), Anesthesia (Dr Orlowski), Pediatrics (Dr Orlowski), and Pathology (Dr Tubbs), Cleveland (Ohio) Clinic Foundation.

Reprint requests to Department of Otolaryngology and Communicative Disorders, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (Dr Levine).

operating room on the fourth postoperative day.

Histologic evaluation of the tonsillar and adenoid tissue revealed severe follicular hyperplasia. Cultures for aerobic and anaerobic bacteria, fungi, and acid-fast bacteria were negative.

Postoperatively, the patient has resumed his normal activities; he no longer requires oxygen therapy, and dyspnea and cyanosis occur only with extreme exertion. Twelve months postoperatively, the results of pulse oximetry were significantly improved, and pulmonary function tests revealed only a restrictive defect related to severe chest wall deformity. The CD4 lymphocyte count was 300/mL.

COMMENT

As of July 1989, there were fewer than 400 reported cases of acquired immunodeficiency syndrome in adolescents (ages 13 to 19 years) in the United States; the number of HIV-infected adolescents who have not yet developed the acquired immunodeficiency syndrome is unknown. Our patient contracted the HIV infection from blood transfusions between 1983 and 1985. It appears that the majority of HIV infections in the adolescent age group are transfusion related, often affecting hemophiliacs. However, it is possible that sexual transmission and intravenous drug-related infections may be important in the near future.

Laboratory assessment of patients with HIV infection reveals positive antibody tests by enzyme-linked immunosorbent assay and Western blot analysis, blood cultures positive for HIV, inversion of T-helper–suppressor cell ratio, and impaired cellular and humoral immune function.[2] The virus is often latent for many years before symptoms develop, but 3-year survival is rare in symptomatic individuals. Death usually results from opportunistic infections, of which *Pneumocystis carinii* pneumonia is the most common.[3]

The frequent occurrence of recurrent otitis media and chronic sinusitis in HIV-infected children is secondary to B-cell dysfunction, with the patient being susceptible to upper airway infection from *Streptococcus pneumoniae*, *Haemophilus influenzae*, and other upper respiratory tract organisms. Infection with these bacterial agents is less common in adult HIV infection, because of the production of protective antibodies prior to the development of immunodeficiency.[4] To our knowledge, the role of enlarged tonsils and adenoids in the development of otitis media and chronic sinusitis in the pediatric population has not been documented.

Our patient presented with progressive dyspnea associated with tonsillar enlargement and upper airway obstruction. There was no evidence of lower airway involvement in the form of *P carinii* pneumonia. Tonsillar enlargement with upper airway obstruction has been associated with pulmonary hypertension, cor pulmonale, and right ventricular failure in normal children.[5] Similarly, our patient's hypoxia and the obstructive component of pulmonary disease and dyspnea at rest resolved with tonsillectomy and adenoidectomy. The risk of postobstructive pulmonary edema must be considered in these patients; the use of postoperative positive end-expiratory pressure will prevent this sequela.[6] Bleeding occurred in our patient even though the results of preoperative coagulation studies were normal. The use of antibiotic prophylaxis is supported by (1) the heavy growth of multiple microorganisms in normal patients who have posterior nasal packs and who are not receiving antibiotic therapy, and (2) the risk of toxic shock syndrome from nasal packs.[7]

Head and neck manifestations of HIV infection are common; 41% of patients in one series initially presented with involvement in this region.[3] The differential diagnosis of tonsillar and adenoid enlargement in patients with HIV should include recurrent bacterial infection, chronic candidiasis and other opportunistic infections, Kaposi's sarcoma, lymphoma, and benign lymphoid hyperplasia. Acute or recurrent bacterial infection is accompanied by fever, pharyngitis, dysphagia with poor oral intake, and tonsillar inflammation with exudate. Neonatal HIV infection is associated with impaired humoral immunity and poor response to bacterial infections.[4] Oral cavity or esophageal candidiasis is present in 31% of HIV infections at initial presentation.[3] The remainder of patients will develop mucosal *Candida* infection during antimicrobial therapy for other opportunistic infections. Isolated involvement of Waldeyer's ring is unusual, and lymphoid enlargement due to *Candida* infection is atypical. Consideration of a number of opportunistic infections requires appropriate cultures and stains for aerobic and anaerobic bacteria, mycobacteria, viruses, protozoa, fungi, and acid-fast bacteria.

Kaposi's sarcoma in the oral cavity is present on initial evaluation in a significant number of adults with HIV infection.[3] The intraoral sites have a characteristic bluish angiomatous quality. The palate is the most common site, although tonsillar involvement is not uncommon. Histologic analysis reveals the predominant cell to be spindle-shaped; it also reveals the formation of narrow vascular channels. Three distinct patterns have been described: (1) predominant spindle cells, (2) spindle cell and vascular endothelial cell mixture, and (3) anaplastic cells with necrosis.

Benign enlargement of the adenoids, tonsils, or lymph nodes was detected in 15 of 43 HIV-seropositive patients by computed tomography and/or magnetic resonance imaging.[8] Pathologic evaluation revealed benign follicular hyperplasia in eight patients, site unspecified. Benign lymphadenopathy was uniformly homogeneous in computed tomographic density and magnetic resonance signal intensity. Radiographic assessment may provide information in distinguishing benign enlargement of Waldeyer's ring from malignant lymphadenopathy.

Changes in lymph node morphological features described in parotid and cervical specimens in patients with HIV infection may be similar to Waldeyer's ring lymphoid tissue involvement. Several histopathologic patterns have been described, including florid follicular hyperplasia, paracortical hyperplasia, angioimmunoblastic lymphadenopathy, and lymphocyte depletion.[9]

Ryan et al[10] distinguish between hyperplastic and atrophic histologic patterns in HIV-associated salivary gland lymphadenopathies. The hyperplastic pattern consists of lymphoid follicles with enlarged germinal centers, which are irregularly shaped, voluminous, and coalescent. A diffuse, mixed inflammatory infiltrate invades the germinal center. This represents the acute pattern of lymphadenitis of HIV infection. The chronic pattern is characterized by small, atrophic lymphoid follicles, inconspicuous germinal centers, and marked vascular proliferation.

In a recent study, pathologic specimens from periparotid lymph nodes revealed benign lymphoid hyperplasia and a uniform follicular hyperplasia.[11] Follicular hyperplasia may suggest the acute phase of the process. This may reflect some preservation of immune status, consistent with the clinical stage of the patient.

An association between a rapidly enlarging cervical mass and Burkitt's lymphoma was noted in 13 patients with HIV infection.[3] A subsequent report documented a diffuse, large cleaved-cell (non-Hodgkin's) lymphoma involving lymph nodes and bone marrow associated with HIV infection.[10] Impaired immune function may predispose to malignant lymphomas.

CONCLUSIONS

Our patient presented with upper airway obstruction due to HIV-associated tonsillar and adenoid lymphadenopathy. He tolerated this condition poorly because of simultaneous scoliosis-induced restrictive pulmonary disease, but he experienced symptomatic relief following tonsillectomy and adenoidectomy.

We would like to thank Janna Kennedy for her assistance in manuscript preparation.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Late Recovery of Auditory Comprehension in Global Aphasia
Margaret A. Naeser, PhD; Ann Gaddie, MS; Carole L. Palumbo; Denise Stiassny-Eder, MS (*Arch Neurol*. 1990;47:425-432)

The Contribution of Multicenter Trials to Stroke Prevention and Treatment
H. J. M. Barnett, MD (*Arch Neurol*. 1990;47:441-445)

Controlled Clinical Trials in Cerebrovascular Disease
John Marshall, MD (*Arch Neurol*. 1990;47:444)

Multicenter Trials in Stroke
Vladimir Hachinski, MD, DSc (*Arch Neurol*. 1990;47:445)

Migraine-Related Stroke in the Context of the International Headache Society Classificaiton of Head Pain
K. M. A. Welch, MD; Steven R. Levine, MD (*Arch Neurol*. 1990;47:458-462)

Letters to the Editor

Adenotonsillectomy

To the Editor.—Dr David Austin[1] is to be commended for his courageous second look at adenotonsillectomy vis-a-vis chronic serous otitis media/recurrent bacterial otitis media. A number of senior otolaryngologists have, for decades, advocated an adenotonsillectomy approach to recurrent bacterial otitis media. Their work was, unfortunately, drowned out by the rush to tympanostomy tube placement. In a way, the tympanostomy tube with its complications of otorrhea, extrusion, cholesterol pearl formation, and persistent perforations represents a double-edged sword. Crying, traumatized, unhappy pediatric otologic patients have "enslaved" two generations of otolaryngologists.

Adenotonsillectomy has proven to be the procedure of choice for the following conditions:

- upper airway compromise [2-4]
- obstructive sleep apnea[2,5,6]
- upper airway compromise with secondary cor pulmonale[2,7]
- aberrant dentofacial development[8-10]
- recurrent bacterial adenotonsillitis
- chronic serous otitis media/bacterial otitis media
- some cases of enuresis
- excessive daytime sleepiness[3]
- retarded intellectual and physical growth[3]

It is indeed unfortunate that third-party health insurance carriers pay so poorly for such a wonderful procedure. When an office "dizzy work-up" with ENG and BAER can command $1000 and an adenotonsillectomy yields $450, something is tragically wrong with our system.

Dr Austin is to be commended for his courageous stand on this vital issue. All otolaryngologists should join in an effort to restore some economic sense into the adenotonsillectomy reimbursement issue.

George M. Meredith, MD
Virginia Beach, Va

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In Reply.—I wish to thank Dr Meredith for his kind statements. He has rightly pointed out that tonsillectomy and adenoidectomy are procedures that are properly indicated in many conditions. Chronic infection of the tonsils and adenoids leads to poor nutrition and growth, and to loss of resistance to acute intermittent infection. To see a child flourish after an indicated adenotonsillectomy is a significant reward. How to transmit this knowledge to our pediatric colleagues is a challenge facing our specialty.

The second point raised by Dr Meredith, the economic inequity of third-party reimbursement, is yet another challenge. The common feeling that adenotonsillectomy is a minor procedure, best performed as an outpatient, certainly contributes to this problem. Why is it that I approach a tonsillectomy-adenoidectomy with far more trepidation than a mastoidectomy?

I again thank Dr Meredith for raising these important considerations.

David F. Austin, MD
Idaho Falls, Idaho

Blood Use in Head and Neck Tumor Surgery

To the Editor.—I agree with McCulloch and colleagues' endorsement[1] of the use of autologous blood as a reasonable option for the majority of patients with head and neck tumors, and would like to further emphasize the immunosuppressive considerations.

Evidence exists for both clinical and laboratory studies that perioperative allogeneic blood transfusions are immunosuppressive. This may be clinically advantageous in transplantation patients, but is undesirable in nontransplantation patients because it may increase the risk of infectious disease complications and the risk of tumor recurrence in patients undergoing curative resection for cancer. While some studies may suggest that perioperative blood transfusions adversely affect disease-free survival following curative resection for malignancy, the results are equivocal.

However, there are several studies that show a strong association of allogeneic blood transfusions and resistance to infections. In a series of recent animal studies, it has been shown that allogeneic blood transfusions can increase a patient's susceptibility to exogenous infection.[2]

Retrospective human studies provide support for the idea that transfusions increase susceptibility to infection. Tartter et al[3] found a 25% incidence of infectious complications in colon cancer patients administered perioperative blood transfusions as opposed to an incidence of only 7% in patients not receiving transfusions. This effect was shown to be independent of age, sex, blood loss, degree of tumor differentiation, lymph node involvement, duration of operation, and the tumor size. Several other studies have shown that blood transfusions were associated with increased rates of pneumonia, sepsis, and other infectious complications,[4,5] although they were retrospective and somewhat limited in that the indication for blood transfusions may have been associated with other factors (eg, severity of illness). Prospective studies examining blood transfusions independent of confounding factors will be needed to answer these questions.

Nevertheless, data from the retrospective clinical studies and experimental animal models together sharply suggest that an immunosuppressive effect from blood transfusions results in an increased susceptibility to infection. This consideration further supports limiting the use of allogeneic blood transfusions and increasing the routine autologous blood donation preoperatively in the appropriate population.

George H. Landis, MD
St Paul, Minn

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Caution Indicated in Prescribing Ciprofloxacin

To the Editor.—I agree with Rubin and coworkers[1] whose article appeared in the September 1989 issue of the Archives that ciprofloxacin is an effective treatment against *Pseudomonas aeruginosa* infection of the ear in cases that are diagnosed as "malignant external otitis."

For your information, I had the privilege of working as a resident under J. Ryan Chandler, MD, in the days when "malignant external otitis" was a uniformly fatal disease despite extensive surgical and, at that time, up-to-date medical treatment.[2,3] With the advent of modern intravenous antibiotic chemotherapy (gentamicin, carbenicillin), patients with malignant external otitis would be hospitalized for 6 weeks while therapy was ongoing. Most patients survived this treatment without extensive surgery.

Today, with the oral treatment of patients with malignant external otitis, using ciprofloxacin on an outpatient basis for 4 to 6 weeks, we are able to cure these patients who, 20 years ago, would have died. This is a real miracle of modern medicine.

My concern, which is shared by all physicians who have learned by history, is that ciprofloxacin (Cipro) will be used to treat many infections not of the same severity nor with the same malignant potential as malignant external otitis. All too often in the history of antibiotic therapy, eg, penicillin and tetracycline in the treatment of *Staphylococcus*, the organisms develop resistance to the antibiotic that was originally efficacious. This would be a tragedy if it happened in the treatment of cases of malignant external otitis and *P aeruginosa.*

The otolaryngologists should sound the warning to our medical colleagues that ciprofloxacin should be primarily reserved for cases of proven cultures of *P aeruginosa*, particularly in diabetic patients with accompanying *Pseudomonas* ear infections or in other specifically indicated situations as dictated by culture and sensitivity reports. The dilemma is that since ciprofloxacin is such a powerful antibiotic, it could be prescribed in cases that do not carry the malignant potential that *P aeruginosa* infections have in the diabetic patient.

There needs to be awareness that resistance to *Pseudomonas* by ciprofloxacin is a real potential danger unless we exercise extreme caution in its prescription and reserve its use to those cases with culture and sensitivities that dictate its indications and/or ear canal infections with *Pseudomonas* in a diabetic patient.

Robert E. Pickard, MD
Miami, Fla

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In Reply.—Dr Pickard makes an excellent clinical point, and we agree.

Jennifer Rubin, MD
Victor L. Yu, MD
Pittsburgh, Pa

In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Frequency of Dysplastic Nevi Among Nevomelanocytic Lesions Submitted for Histopathologic Examination: Time Trends Over a 37-Year Period
Raymond L. Barnhill, MD; Hiromaro Kiryu, MD; Arthur J. Sober, MD; Martin C. Mihm, Jr, MD (*Arch Dermatol.* 1990;126:463-465)

Anatomic Distribution of Acquired Melanocytic Nevi in White Children: A Comparison With Melanoma: The Vancouver Mole Study
Richard P. Gallagher, MD; David I. McLean, MD; C. Paul Yang, MD; Andrew J. Coldman, PhD; Hulbert K.B. Silver, MD; John J. Spinelli, MSc; Marjorie Beagrie, MA (*Arch Dermatol.* 1990;126:466-471)

Behavior Modification Obtained by Sun Protection Education Couples With Removal of a Skin Cancer
June K. Robinson, MD (*Arch Dermatol.* 1990;126:477-481)

The Effect of Topical Tretinoin on Dysplastic Nevi: A Preliminary Trial
Libby Edwards, MD, Philip Jaffe, MD (*Arch Dermatol.* 1990;126:494-499)

News and Comment

Genetics of Hearing Impairment.—The New York Academy of Sciences and the Deafness Research Foundation announce that they will sponsor a conference entitled "Genetics of Hearing Impairment" from September 24 through 26, 1990, at the Sheraton Centre, New York, NY. All of those concerned with hearing impairment will find substantial information in the conference as it will concern hereditary human hearing impairment at all levels. These will include molecular genetics, biochemistry, anatomy, gene expression, epidemiology, clinical diagnosis, sociology, and ethics. The conference chairman will be Robert J. Rubin, MD, Department of Otolaryngology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY. For further information, contact Conference Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212) 838-0230; fax (212) 888-2894.

The Third International Head and Neck Oncology Research Conference.—The American Society for Head and Neck Surgery will sponsor the Third International Head and Neck Oncology Research Conference, September 26 through 28, 1990, at the Tropicana Hotel, Las Vegas, Nev. The conference chairmen will be Thomas E. Carey, PhD, and Gregory T. Wolf, MD, Department of Otolaryngology, University of Michigan, Ann Arbor. The major emphasis on this conference will be workshop discussions concerning ongoing basic and clinical research efforts. Participation is invited from investigators active in areas of both basic and clinical head and neck oncologic research related to cell biology, immunology, pharmacokinetics, chemotherapy, radiation therapy, surgery, virology, molecular genetics, and innovative therapeutic approaches, such as photoradiation, accelerated fraction radiation, monoclonal antibody therapy, and adoptive immunotherapy. For further information, contact Gayle Fox, Program Assistant, Office of Continuing Medical Education, G-1100 Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.

Continuing Medical Education: Trends in Electrophysiologic Assessment: Intraoperative Applications.—The Office of Continuing Medical Education of the University of Michigan Medical School is sponsoring an upcoming course entitled "Recent Trends in Electrophysiologic Assessment: Intraoperative Applications." This course, which will be held on September 7 and 8, 1990, at the Towsley Center, Ann Arbor, Mich, will provide a comprehensive overview of state-of-the-art clinical electrophysiology in intraoperative applications. In addition to didactic presentations, demonstration of facial nerve and auditory functioning monitoring will be presented. The emphasis of the course will be a practical approach for practitioners, presented by practitioners. The course is targeted for clinicians having prior experience with evoked potentials who wish to learn or become updated on the applications covered by this course. Thirteen credit hours will be offered; the course director is Paul R. Kileny, PhD, Department of Audiology and Electrophysiology, University of Michigan Medical School. For further information, contact Betty Phillips, Program Assistant, Office of Continuing Medical Education, G-1100 Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.

Head and Neck Surgery Workshop.—The Society of Head and Neck Surgeons announces that its Sixth Annual Workshop will be held on October 6 and 7, 1990, at the University of California at San Francisco.

Resident's Page

ROBERT E. FECHNER, MD, SECTION EDITOR

University of Virginia School of Medicine, Charlottesville

PATHOLOGIC QUIZ CASE 1

Antoine E. Tarazi, MD, David W. Eisele, MD, Baltimore, Md

During the summer, a 74-year-old white woman with a history of moderate sun exposure noted a nonpruritic left cheek lesion of approximately 1 month's duration. She had no history of skin malignancy.

On physical examination, a 3-mm, flat, keratotic lesion was noted on the lower part of the cheek. The lesion was nonpigmented and solitary.

An excisional biopsy of the mass was performed. Photomicrographs of the surgical specimen are shown in Figs 1 and 2.

What is your diagnosis?

PATHOLOGIC QUIZ CASE 2

Avi Shupak, MD; Nehama Uri, MD; Elhanan Greenberg, MD; Judith Kelner, MD; Walter S. Meyer, MD, Haifa, Israel

A 7-year-old-boy presented for evaluation of right facial paresis, which had slowly progressed over the last 3 years. The patient had not experienced any worsening of his hearing and had no complaints of tinnitus or vertigo. There was no history of chronic otitis media, ear surgery, or skull trauma. Physical examination revealed a bluish-gray intact right tympanic membrane, whose posterior part was pulsating in accordance with the arterial pulse. Valsalva's maneuver caused bulging of the right tympanic membrane, when the pulsation disappeared. An audiogram indicated right pure tone average of 30 dB with normal bone conduction and 100% speech discrimination. The right tympanogram curve was of type B. Axial and coronal computed tomography revealed a hypodense tissue originating in the right geniculate fossa area, spreading to the epitympanum and mesotympanum, with erosion of the bony lateral semicircular canal, the horizontal segment of the fallopian canal (Fig 1), the cochlear wall at the promontorium, and the lateral wall of the epitympanum (Fig 2). On operation, the mastoid air cells and tympanic cavity were seen to fill quickly with a clear watery fluid. The posterior and superior bony walls of the external auditory canal were very thin and friable, as was the bony lateral semicircular canal. The incus and malleus, which were found to be largely eroded, had been extracted. The fallopian canal was dehiscent superior to the oval window and was engulfed by a grayish tissue. Clear fluid was flowing around this tissue down over the horizontal portion of the facial nerve and into the middle ear. The tissue was followed anteriorly in the attic and was excised near the geniculate ganglion. The leakage area was packed with fat taken from the ear lobule and was covered with temporal fascia. Low-and high-power hematoxylin-eosin-stained sections illustrate the histopathologic features (Figs 3 and 4).

What is your diagnosis?

PATHOLOGIC QUIZ CASE 1

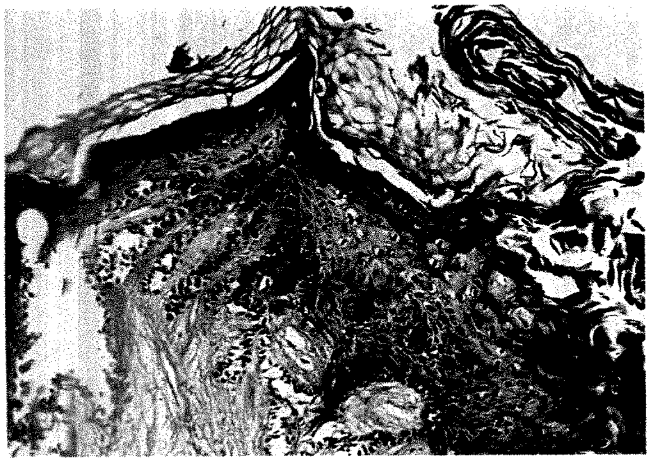

Figure 1.

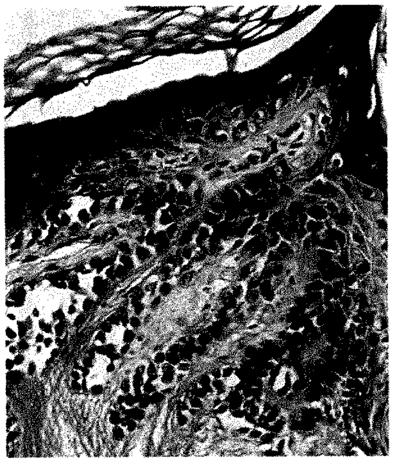

Figure 2.

PATHOLOGIC QUIZ CASE 2

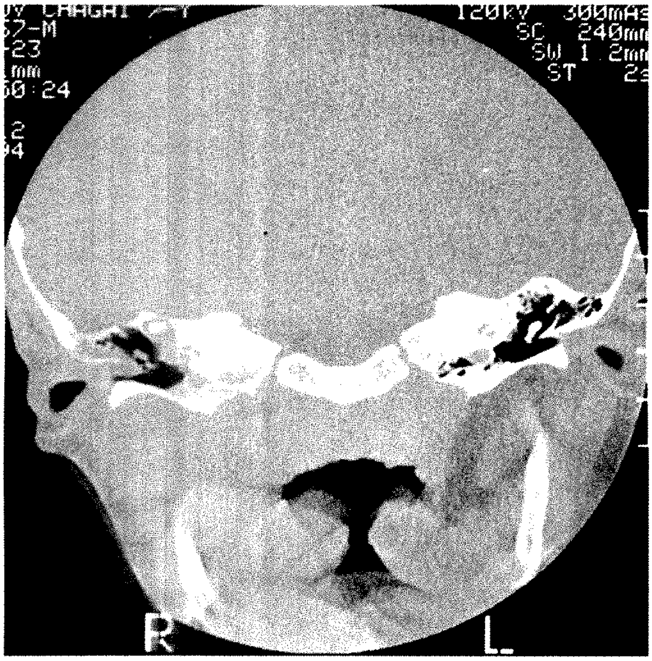

Figure 1.

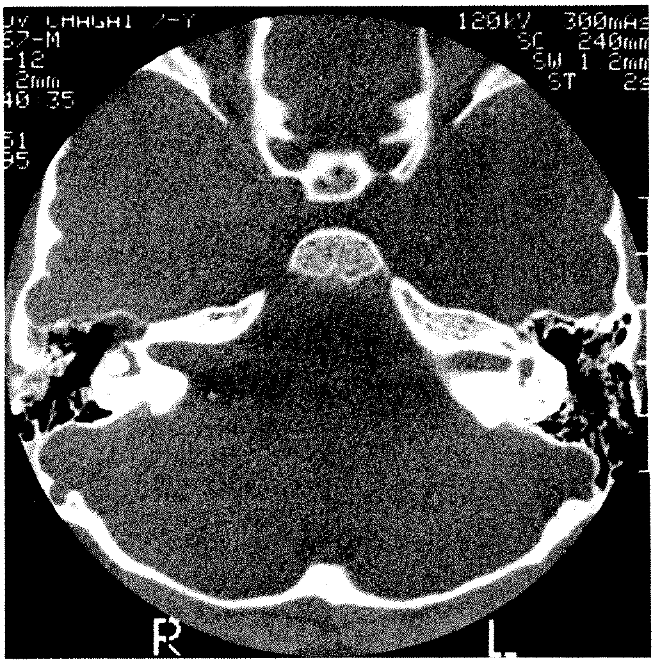

Figure 2.

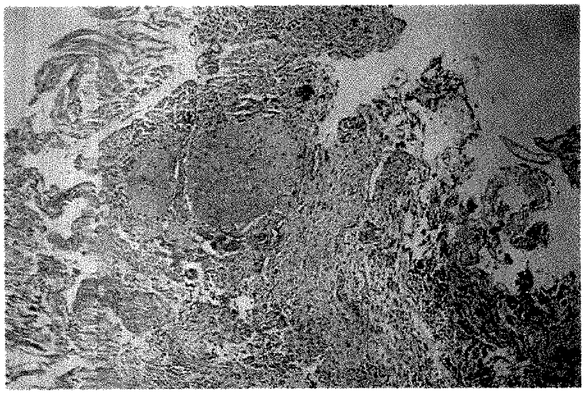

Figure 3.

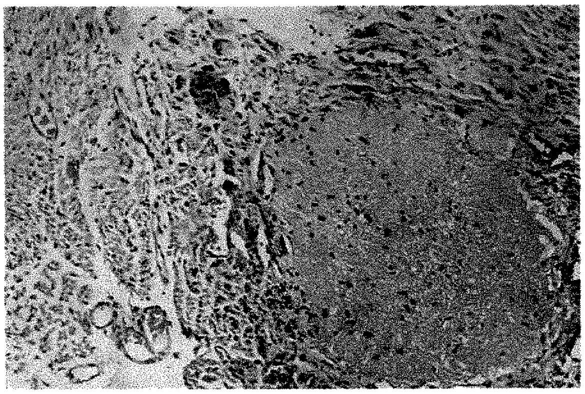

Figure 4.

Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 1

Pathologic Diagnosis: Transient acantholytic dermatosis. Transient acantholytic dermatosis, also known as Grover's disease, was originally described by Grover[1] in 1970. This entity typically presents as pruritic polymorphic papules and vesicles with excoriations over the back, chest, and lumbar area. Less commonly the scalp, neck, and thighs are involved.[2] The lesions are usually sparse and discrete. The vast majority of cases reported in the literature involve fair-skinned men older than 40 years. The course of the disease is usually brief. The lesions persisted from 2 weeks to 3 months in two of three patients described in one report.[2]

Four main histologic patterns of transient acantholytic dermatosis are described: Darier's type, Hailey-Hailey type, spongiotic type, and pemphigus type.[2] Two or more of these forms can occur simultaneously. The unifying feature to all varieties is acantholysis, or loss of cohesion of epidermal cells. Acantholysis can appear at any level of the epidermis and can be accompanied by dyskeratosis. Figure 1 shows hyperkeratosis, acanthosis, and acantholysis of the granular suprabasal layers of the epidermis. A discrete focus of acantholysis is shown in Fig 2.

The clinical differential diagnosis includes pemphigus, acne, seborrheic dermatitis, miliara rubra, folliculitis, scabies, dermatitis herpetiformis, actinic keratosis, and basal and squamous carcinoma. These are differentiated from Grover's disease histopathologically. In the case of pemphigus, the acantholysis usually involves the entire specimen, in contrast to the circumscribed involvement of Grover's disease.[2] In addition, pemphigus may be differentiated from transient acantholytic dermatosis by immunofluorescence studies.

The pathogenesis of Grover's disease is unknown, but a cause and effect relationship to heat and sweat has been proposed.[3] Sweat and heat are hypothesized to cause acantholysis in Grover's disease, the former by the action of urea and the latter through an enzymatic factor released in the epidermis.[3] Often, skin lesions are noted during hospitalization and prolonged bed rest.[3,4] In one series, coexistent solar effects on the skin, ranging from solar keratosis to basal and squamous cell carcinoma, were noted on sun-exposed areas of the body in 23 of 24 patients with transient acantholytic dermatosis.[4]

Advocated treatment for transient acantholytic dermatosis is topical fluorinated steroids in most cases. In addition, oral vitamin A therapy (150 000 U three times for a day for 2 weeks) has produced a satisfactory clinical response.[4,5] Antihistamines apparently have not been beneficial for the control of pruritus.[4]

Since first described by Grover,[1] there has been increased awareness of this disease, with more cases reported each year. Diagnosis requires a high index of suspicion and should be considered for pruritic skin lesions in patients older than 40 years. Patients occasionally give a history of previously excised basal and squamous cell carcinomas. New skin lesions, therefore, require thorough evaluation because of the concern for tumor or recurrence of carcinoma.

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Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 2

Pathologic Diagnosis: Congenital middle ear encephalocele (CMEE).

An encephalocele may be defined as a protrusion of brain substance connected to the rest of the brain by a pedicle. Numerous other terms have been used to describe this condition in the middle ear region, including brain fungus, meningoencephalocele of the mastoid, dural hernia, brain hernia, brain prolapse, endaural cerebral hernia, and mastoiditis cerebri.[1,2] Middle ear encephalocele can be related to trauma due to previous otologic surgery, chronic middle ear infection, temporal bone fracture, or congenital temporal bone abnormalities.[3] In the early 20th century, herniation of the cerebellum or temporal lobe into the tympanic cavity or mastoid was a well-recognized postmastoidectomy complication, which was particularly associated with otogenic brain abscess drainage. The introduction of antibiotics, the operating microscope, and other modern surgical equipment and techniques led to the reduction of intracranial complications secondary to middle ear infections and of the anatomic defects due to mastoid surgery.[1-4] Still, the acquired causes are by far the more common: CMEE was found in only 31 of 141 middle ear encephalocele cases reported over the last 40 years.[4]

The pathogenesis of CMEE is not

clear. It is universally agreed that defects in bone and dura are essential prerequisites for the brain to herniate. Pneumatization of the temporal bone begins approximately at the 34th week of gestation and is not completed until adulthood.[1] Bone remodeling, occurring in accordance with pneumatization, might explain the high rate of tegmen dehiscence found in 21% of postmortem skulls examined.[5] Although most encephaloceles expand through tegmen defects, they may also protrude through a posterior fossa bony plate perforation.[1-4,6] As normal dura is extremely strong and capable of supporting the brain over significant bony defects,[1,7] it is assumed that CMEE develops when the now-exposed dura has been weakened by repeated latent middle ear infections.[1,3] Local temporal lobe cerebritis, caused by the spread of middle ear infection through the weakened dural barrier, leads to increased intracranial pressure, thus facilitating brain herniation.[1,2] It has also been suggested that pacchionian bodies, or arachnoidal granulations, play a role in the pathogenesis of CMEE.[8]

Histologically, the brain tissue herniating into the middle ear does not have dural covering or any arachnoidal sheath.[1,3] In the present case, it consists of mature neural tissue embedded within disoriented nonmyelinated nerve fibers. The brain tissue frequently shows microglial proliferation and is surrounded by a pseudocapsule consisting of fibrovascular reaction, as demonstrated in Figs 3 and 4. The preoperative diagnosis of CMEE requires a high index of suspicion, and many cases reported were recognized only during surgery.[1,2,9] The most common presenting symptoms in CMEE are recurrent or persistent cerebrospinal fluid (CSF) otorrhea and/or rhinorrhea, a history of intermittent serous otitis media, conductive hearing loss, and, occasionally, recurrent meningitis. Facial paresis, as in our patient, and temporal lobe seizures are rarely encountered.[1,2,4,9,10] Physical examination when the eardrum is intact, in which case no spontaneous otorrhea is observed, might reveal a pulsating intratympanic mass and effusion.[1-3,9]

Whenever CSF otorrhea is a presenting symptom, the acquired causes of that otorrhea, including previous otologic surgery, skull base trauma, and chronic middle ear infection with cholesteatoma, should be considered. If these are excluded, the possibility of a congenital defect in the tegmen or posterior fossa bony plate, with the associated occurrence of encephalocele, should be raised.[10] Congenital labyrinthine fistulas through the petromastoid canal, the wide cochlear aqueduct, the facial canal, or Hyrtl's fissure, which is a bony cleft leading from the posterior fossa to the inferior aspect of the round window, are another rare cause of congenital CSF otorrhea.[6]

High-resolution computed tomography can reveal a tegmen antri or tympanic defect, opacity of the tympanic cavity, and middle ear bony structure changes secondary to the pulsations of the encephalocele and to the CSF pressure, as demonstrated in Figs 1 and 2.[4,9] It has been suggested that magnetic resonance imaging can provide preoperative information regarding the contents of the herniation.[11] Intrathecal injection of the dyes iophendylate, metrizamide, fluorescein, and indigo carmine, as well as the radioactive tracers technetium 99, indium 111, and ytterbium 169, may be used for the diagnosis of CSF otorrhea.[2,9,10]

Middle ear encephalocele tissue is physiologically nonfunctioning; thus, it can be excised without causing any neurologic deficit. Surgical repair of the dural and bone defects should be carried out at the same time in order to separate the cranial cavity from the upper respiratory tract.[1-4] The herniated brain can be excised and the tegmen defect sealed from below employing mastoidectomy techniques, intradural or extradural middle fossa craniotomy, or the combined middle fossa craniotomy-mastoid approach, repairing the dehiscence from above.[1-4,9,10]

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Residents and fellows in otolaryngology are invited to submit quiz cases for this section and to write letters to the ARCHIVES *commenting on cases presented. Quiz cases should follow the patterns established and must be submitted in duplicate. Photomicrographs must be clear and can include an outline drawing with important structures labeled, especially in the case of histopathology of the ear. Illustrations must be submitted as positive color transparencies (35 mm preferred). Do not submit color prints unless accompanied by original transparencies. Transparencies should be carefully packaged in a separate container. Please do not submit glass-mounted transparencies or the actual glass histology slides. Material for the Resident's Page should be mailed to the Chief Editor.*

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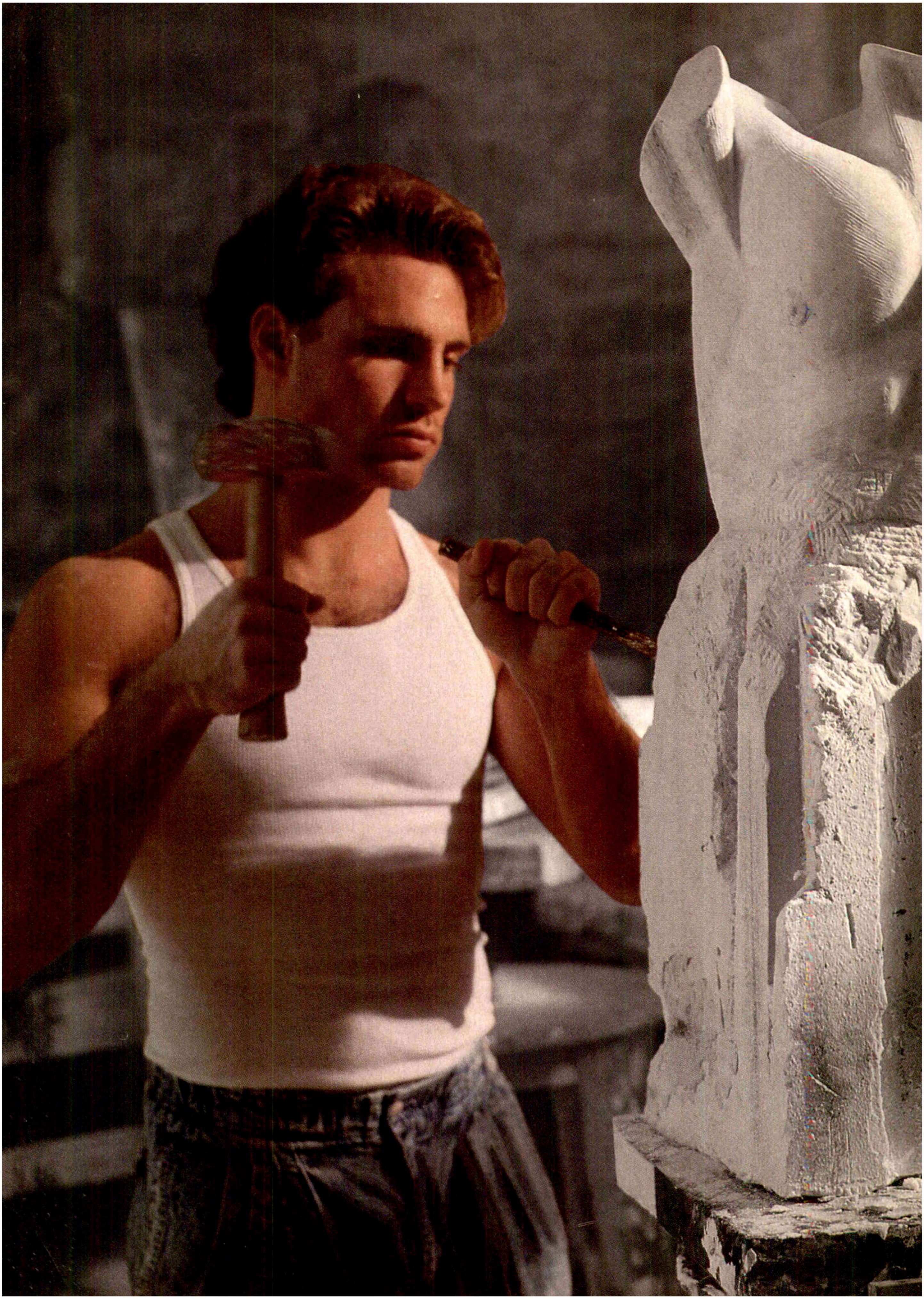

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CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients: Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility: Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C: There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use: Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General: Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia, torsade de pointes and ventricular fibrillation), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

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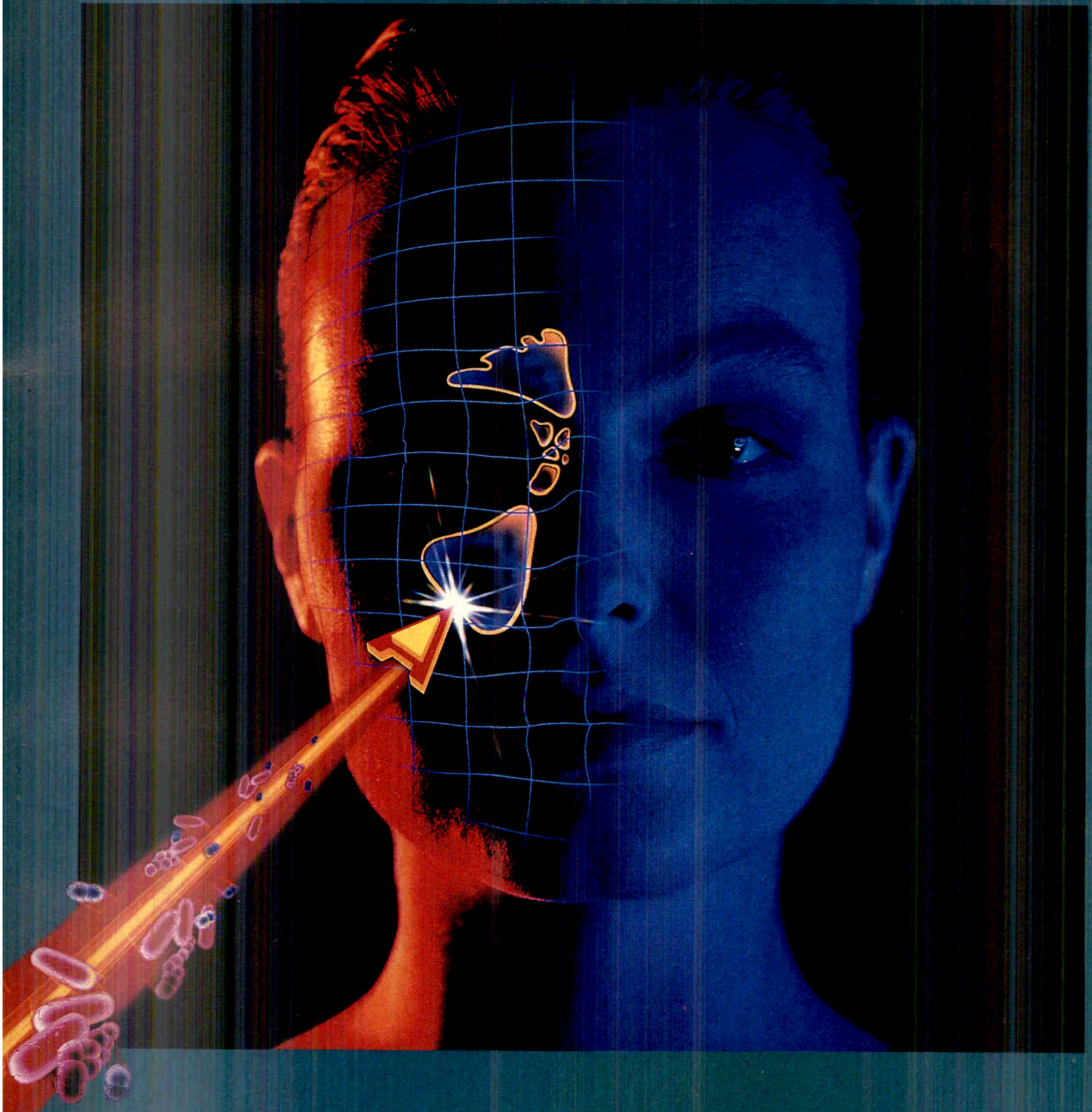

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Indications and Usage: AUGMENTIN* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

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Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to AUGMENTIN treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to AUGMENTIN, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to AUGMENTIN when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While AUGMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN and allopurinol administered concurrently.

AUGMENTIN should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to AUGMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of AUGMENTIN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when AUGMENTIN is administered to a nursing woman.

Adverse Reactions: AUGMENTIN is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT and/or SGPT has been noted in patients treated with ampicillin class antibiotics as well as with AUGMENTIN, but the significance of these findings is unknown. As with some other penicillins, and some cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with AUGMENTIN.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one AUGMENTIN '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one AUGMENTIN '500' tablet every eight hours.

Since both the AUGMENTIN '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two AUGMENTIN '250' tablets are not equivalent to one AUGMENTIN '500' tablet. Therefore, two AUGMENTIN '250' tablets should not be substituted for one AUGMENTIN '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as AUGMENTIN '125' and '250' chewable tablets.

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P.O. Box 1200, Santa Barbara, CA 93102.

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Cary Ear, Nose & Throat Clinic
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Contact:

Department of Pediatric Otolaryngology
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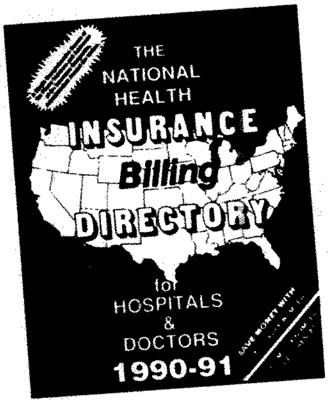

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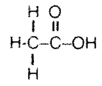

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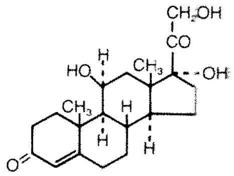

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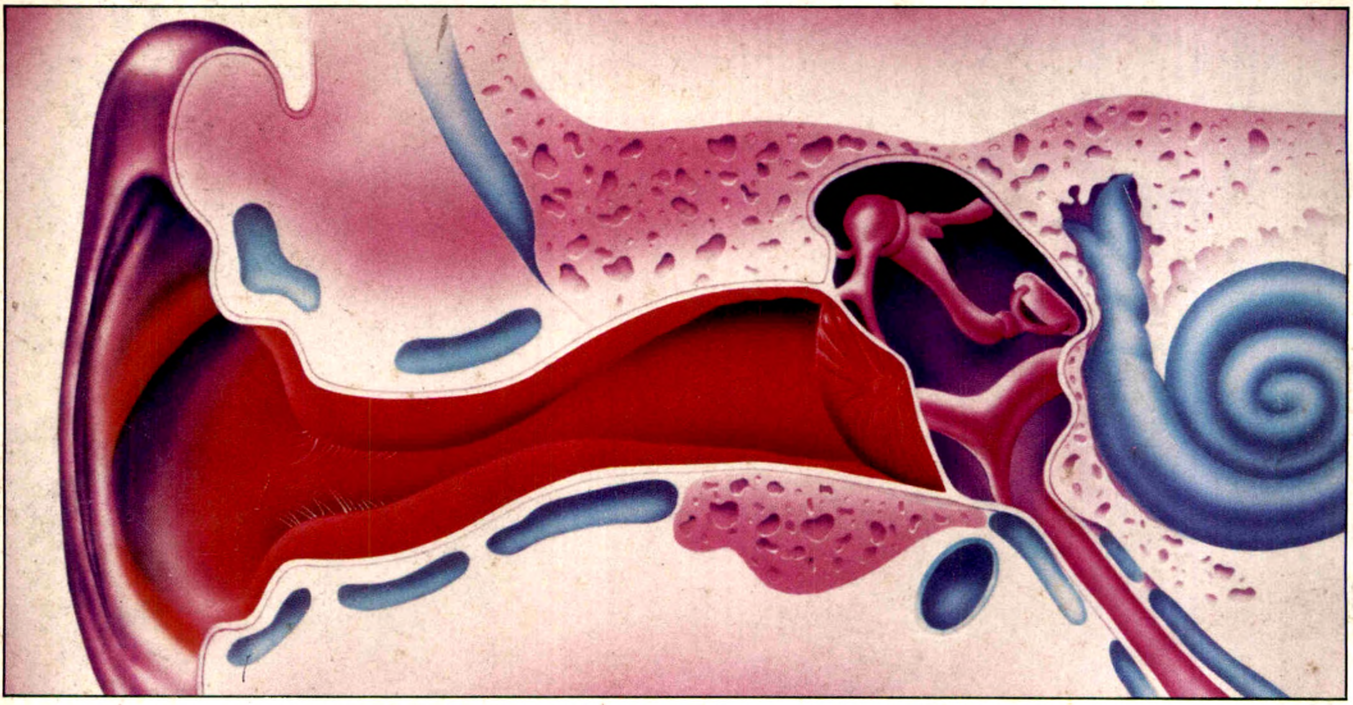

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References: **1.** Ordonez GE, Kime CE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: I. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-polymyxin B otic solutions. *Curr Ther Res*. 1978;23(May suppl):SS3-SS14.
2. Kime CE, Ordonez GE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: II. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-colistin otic solutions. *Curr Ther Res*. 1978;23(May suppl):SS15-SS28.
3. Glassman JM, Pillar J, Soyka JP. Otitis externa: comparative *in vitro* sensitivities of clinical isolates of bacteria and fungi to nonantibiotic and antibiotic otic preparations. *Curr Ther Res*. 1978;23(May suppl):SS29-SS38.

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July 1990
Volume 116, Number 7

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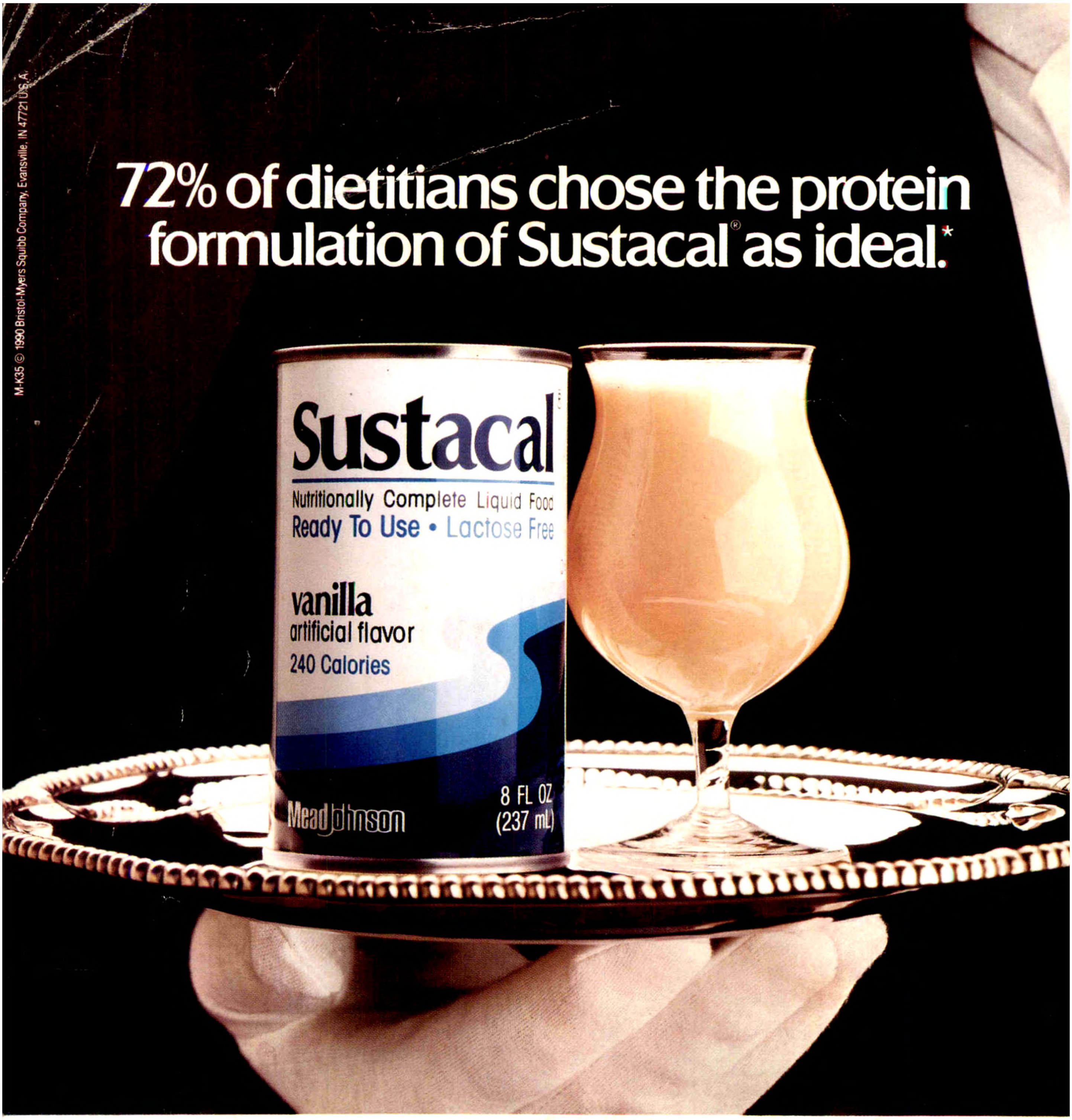
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VOLUME 116, NUMBER 7, JULY 1990

EDITORIAL

Somehow We Have to Stop the Train Wreck: Part 2
Byron J. Bailey, MD, Galveston, Tex 777

EXPEDITED PUBLICATION

Prevention of Microvascular Thrombosis With Controlled-Release Transmural Heparin
Nicholas S. Jones, BDS, FRCS, London, England;
Michael G. Glenn, MD; Lisa A. Orloff, MD; Marc R. Mayberg, MD, Seattle, Wash 779

PAPERS READ BEFORE THE AMERICAN ACADEMY OF FACIAL PLASTIC AND RECONSTRUCTIVE SURGERY

Management of the Paralyzed Lower Eyelid by Implanting Auricular Cartilage
Mark May, MD; Dieter F. Hoffmann, MD;
George F. Buerger, Jr, MD, Pittsburgh, Pa;
David B. Soll, MD, Camden, NJ 786

Management of Animal and Human Bites in the Head and Neck
Fred J. Stucker, MD; Gary Y. Shaw, MD;
Susan Boyd, MD, Shreveport, La;
William W. Shockley, MD, Chapel Hill, NC 789

Dermal Healing After Local Skin Flaps and Chemical Peel
MAJ David K. Hayes, MC, USA; MAJ Michael E. Berkland, MC, USA;
LTC Kweon I. Stambaugh, MC, USA, Fort Sam Houston, Tex 794

Wound Healing: Relationship of Wound Closing Tension to Scar Width in Rats
MAJ Lawrence P. A. Burgess, MC, USA; MAJ Garrison V. Morin, MC, USAF;
CPT Michael Rand, VC, USA; Jafar Vossoughi, PhD;
COL Jeffrey O. Hollinger, DC, USA, Washington, DC 798

Effect of Local Hypothermia on Early Wound Repair
Ramon M. Esclamado, MD; Gregg A. Damiano;
Charles W. Cummings, MD, Seattle, Wash 803

ORIGINAL ARTICLES

Anesthetic Complications of Tympanotomy Tube Placement in Children
Laurie Markowitz-Spence, MD; Linda Brodsky, MD; Naseera Syed, MD;
John Stanievich, MD; Mark Volk, MD, Buffalo, NY 809

Three-Dimensional Images of the Temporal Bone and Experimental Otitis Media in Japanese Monkeys
Tatsuya Fujiyoshi, MD; Tetsuo Watanabe, MD; Goro Mogi, MD, Oita, Japan 813

Blood Viscosity and Sensorineural Hearing Loss
Minka Hildesheimer, PhD; Faai Bloch, MA; Chava Muchnik, PhD;
Moshe Rubinstein, MD, Tel Hashomer, Israel 820

Combination Effect of Hyperthermia and Photodynamic Therapy on Carcinoma
Nobuo Matsumoto, MD; Hitoshi Saito, MD; Norio Miyoshi, PhD;
Kazuo Nakanishi, MD; Masaru Fukuda, MD, Fukui, Japan 824

T2 Glottic Cancer: Recurrence, Salvage, and Survival After Definitive Radiotherapy
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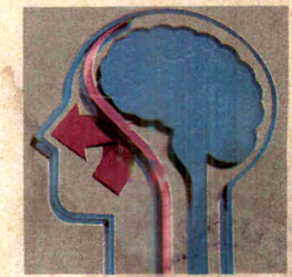

(terfenadine) 60 mg tablets BID
for seasonal allergic rhinitis

Starts fast and lasts

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Before prescribing Seldane, please see Brief Summary of Prescribing Information, which appears on the reverse side.

Seldane®

(terfenadine) 60 mg Tablets

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients: Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility: Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C. There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use: Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General: Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia, torsade de pointes and ventricular fibrillation), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of January, 1990 Y460D
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Cincinnati, Ohio 45215, U.S.A.

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90-1236-03 MNT-074 MDA 085B

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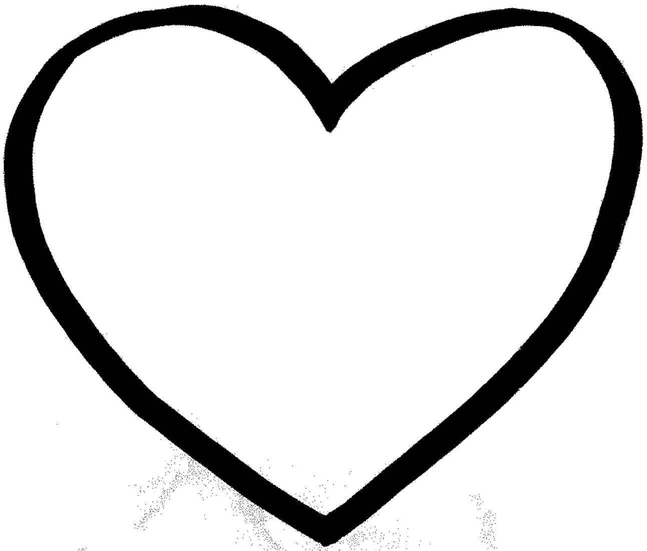

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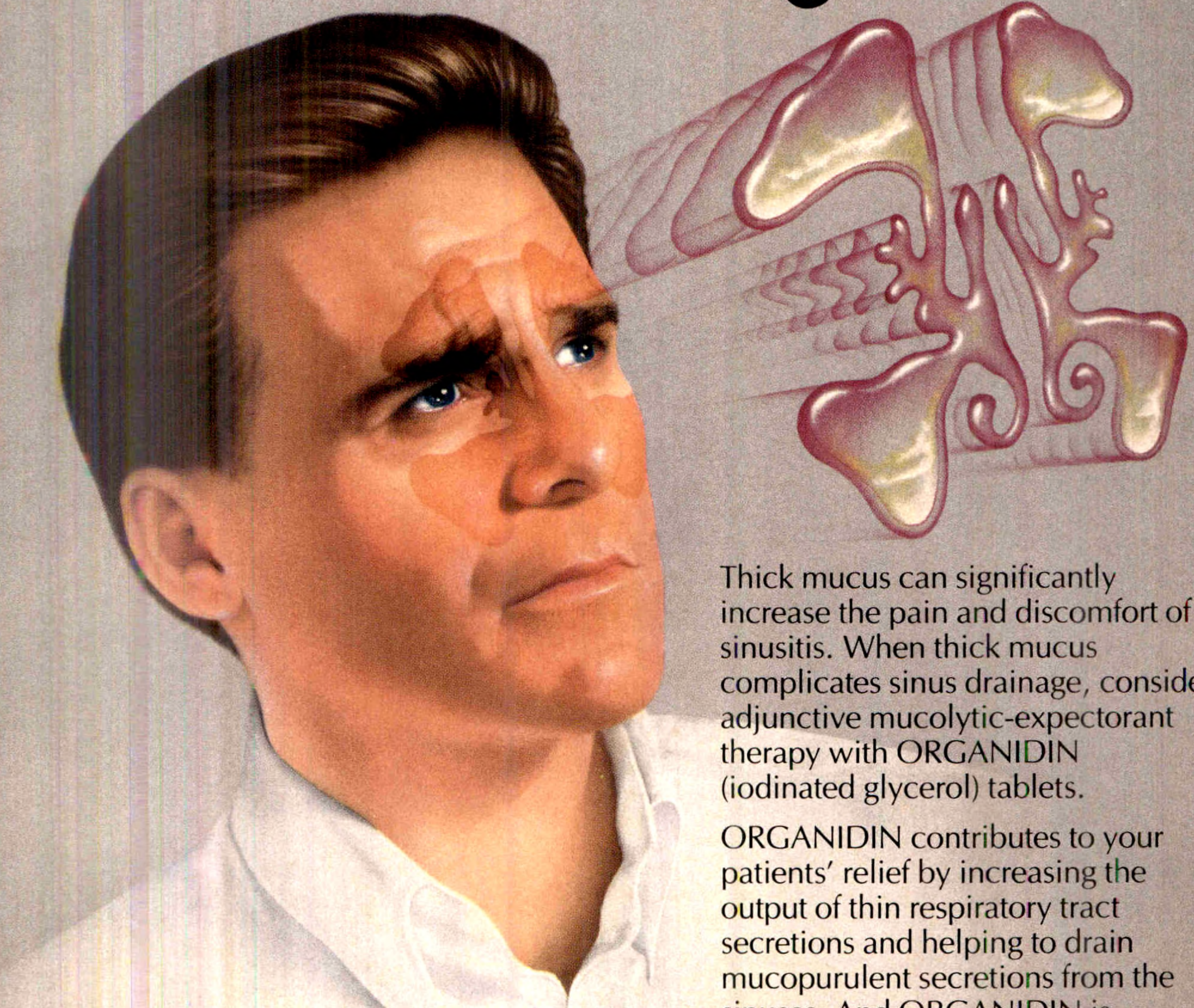
IN SINUSITIS

When thick mucus complicates sinus drainage



Thick mucus can significantly increase the pain and discomfort of sinusitis. When thick mucus complicates sinus drainage, consider adjunctive mucolytic-expectorant therapy with ORGANIDIN (iodinated glycerol) tablets.

ORGANIDIN contributes to your patients' relief by increasing the output of thin respiratory tract secretions and helping to drain mucopurulent secretions from the sinuses. And ORGANIDIN is compatible with the antibiotic of your choice.

ORGANIDIN® Tablets (iodinated glycerol)

Liquefies mucus to promote sinus drainage

WALLACE LABORATORIES
Division of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

Please see following page for prescribing information.

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ORGANIDIN®
(iodinated glycerol)
Tablets, Elixir, Solution

Before prescribing, please consult complete product information, a brief summary of which follows:

INDICATIONS AND USAGE
ORGANIDIN is indicated for adjunctive treatment as a mucolytic-expectorant in respiratory tract conditions such as bronchitis, bronchial asthma, pulmonary emphysema, cystic fibrosis, chronic sinusitis, or after surgery to help prevent atelectasis.

CONTRAINDICATIONS
History of marked sensitivity to inorganic iodides; hypersensitivity to any of the ingredients or related compounds; pregnancy; newborns; and nursing mothers.

The human fetal thyroid begins to concentrate iodine in the 12th to 14th week of gestation and the use of inorganic iodides in pregnant women during this period and thereafter has rarely been reported to induce fetal goiter (with or without hypothyroidism) with the potential for airway obstruction. If the patient becomes pregnant while taking ORGANIDIN, the drug should be discontinued and the patient should be apprised of the potential risk to the fetus.

WARNINGS
Discontinue use if rash or other evidence of hypersensitivity appears. Use with caution or avoid use in patients with history or evidence of thyroid disease.

PRECAUTIONS
General: Iodides have been reported to cause a flare-up of adolescent acne. Children with cystic fibrosis appear to have an exaggerated susceptibility to the goitrogenic effect of iodides.

Dermatitis and other reversible manifestations of iodism have been reported with chronic use of inorganic iodides. Although these have not been reported to be a problem clinically with ORGANIDIN, they should be kept in mind in patients receiving these preparations for prolonged periods.

Drug interactions: Iodides may potentiate the hypothyroid effect of lithium and other antithyroid drugs.

Carcinogenesis, mutagenesis, impairment of fertility: No long-term animal studies have been performed with ORGANIDIN.

Pregnancy: Teratogenic effects: Pregnancy Category X (see Contraindications).

Nursing mothers: ORGANIDIN should not be administered to a nursing woman.

ADVERSE REACTIONS
Reports of gastrointestinal irritation, rash, hypersensitivity, thyroid gland enlargement, and acute parotitis have been rare.

OVERDOSAGE
Acute overdosage with ORGANIDIN has been rare and there have been no reports of any serious problems.

DOSAGE AND ADMINISTRATION
NOTE: Add *Solution* to fruit juice or other liquid. One drop *Solution* equals approximately 3 mg ORGANIDIN.

Adults: *Tablets*—2 tablets 4 times a day, with liquid.
Elixir—1 teaspoonful 4 times a day.
Solution—20 drops 4 times a day.

Children: Up to one-half the adult dosage, based on the child's weight.

HOW SUPPLIED
ORGANIDIN is available as:

Tablets: round, scored, rose-colored tablets, in bottles of 100 (NDC 0037-4224-40).

Elixir: clear amber liquid, in bottles of one pint (NDC 0037-4213-30) and one gallon (NDC 0037-4213-40).

Solution: clear amber liquid, in 30 mL dropper bottles (NDC 0037-4211-10).

Storage: ORGANIDIN Tablets—Store at controlled room temperature. Protect from excessive heat and moisture.

ORGANIDIN Elixir and Solution—Store at controlled room temperature. Protect from freezing and excessive heat.

ORGANIDIN *Tablets* are manufactured by:
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Division of
CARTER-WALLACE, INC.
Cranbury, New Jersey 08512

ORGANIDIN *Elixir* and *Solution* are Distributed by:
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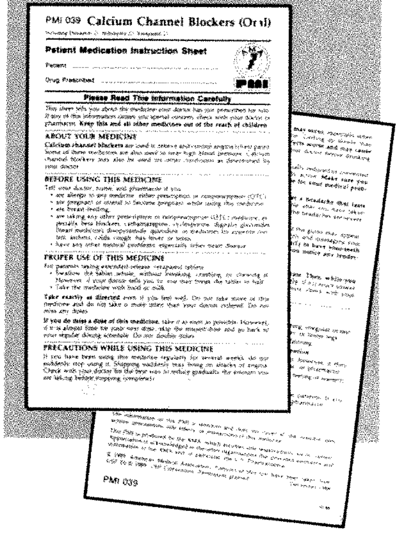

PMI 039 Calcium Channel Blockers (Oral)

Patient Medication Instruction Sheet

Patient

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ABOUT YOUR MEDICINE

BEFORE USING THIS MEDICINE

PROPER USE OF THIS MEDICINE

PRECAUTIONS WHILE USING THIS MEDICINE

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In bacterial sinusitis...

Prescribe

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amoxicillin/clavulanate potassium

First time, first-line for clinical certainty

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Please see brief summary of prescribing information on adjacent page.

Brief Summary of Prescribing Information

AUGMENTIN® amoxicillin/clavulanate potassium

Indications and Usage: AUGMENTIN* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to AUGMENTIN treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to AUGMENTIN, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to AUGMENTIN when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While AUGMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN and allopurinol administered concurrently.

AUGMENTIN should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to AUGMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of AUGMENTIN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore caution should be exercised when AUGMENTIN is administered to a nursing woman

Adverse Reactions: AUGMENTIN is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%), and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT and/or SGPT has been noted in patients treated with ampicillin class antibiotics as well as with AUGMENTIN, but the significance of these findings is unknown. As with some other penicillins, and some cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with AUGMENTIN.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one AUGMENTIN '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one AUGMENTIN '500' tablet every eight hours.

Since both the AUGMENTIN '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two AUGMENTIN '250' tablets are not equivalent to one AUGMENTIN '500' tablet. Therefore, two AUGMENTIN '250' tablets should not be substituted for one AUGMENTIN '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as AUGMENTIN '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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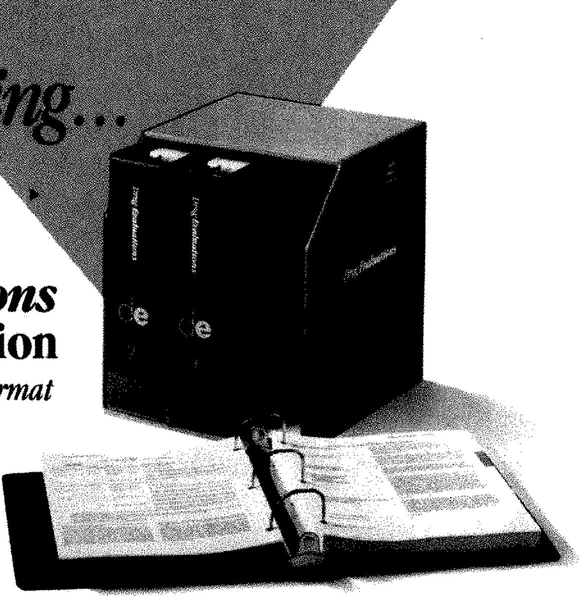

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or Rhinorrhea and Congestion†

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- B.I.D. RYNATAN®-S*
- Convenient Oral Syringe
- By Prescription Only

RYNATAN® B.I.D.
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ach capsule-shaped tablet contains: phenylephrine tannate, 25 mg;
lorpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

RYNATAN®-S* B.I.D.
PEDIATRIC SUSPENSION

Each teaspoonful (5 mL) contains: phenylephrine tannate, 5 mg; chlorpheniramine tannate, 2 mg; pyrilamine tannate, 12.5 mg.

tent pending. RYNATAN®-S is the combination of RYNATAN® Pediatric Suspension
fl oz) and a 10 mL calibrated oral syringe.

hen used for symptomatic relief of coryza and nasal congestion in allergic rhinitis or
e common cold.

ease see the following page for prescribing information.

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WALLACE LABORATORIES
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Cranbury, New Jersey 08512

RYNATAN® B.I.D.
TITRATABLE TABLETS

Each capsule-shaped tablet contains: phenylephrine tannate, 25 mg; chlorpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

RYNATAN®-S*B.I.D.
PEDIATRIC SUSPENSION

Each teaspoonful (5 mL) contains: phenylephrine tannate, 5 mg; chlorpheniramine tannate, 2 mg; pyrilamine tannate, 12.5 mg.

Description RYNATAN® is an antihistaminic/decongestant combination available for oral administration as *Tablets* and as *Pediatric Suspension*. Each tablet contains:

Phenylephrine Tannate	25 mg
Chlorpheniramine Tannate	8 mg
Pyrilamine Tannate	25 mg

Other ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, methylcellulose, polygalacturonic acid, talc.

Each 5 mL (teaspoonful) of the Pediatric Suspension contains:

Phenylephrine Tannate	5 mg
Chlorpheniramine Tannate	2 mg
Pyrilamine Tannate	12.5 mg

Other ingredients: benzoic acid, FD&C Red No. 3, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, sucrose.

Clinical Pharmacology RYNATAN combines the sympathomimetic decongestant effect of phenylephrine with the antihistaminic actions of chlorpheniramine and pyrilamine.

Indications and Usage RYNATAN is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications RYNATAN is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery while using this product.

Drug interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, mutagenesis, impairment of fertility: No long term animal studies have been performed with RYNATAN®.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with RYNATAN. It is also not known whether RYNATAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RYNATAN should be given to a pregnant woman only if clearly needed.

Nursing mothers: RYNATAN should not be administered to a nursing woman.

Adverse Reactions Adverse effects associated with RYNATAN at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Overdosage *Signs and symptoms:* May vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment: Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration Administer the recommended dose every 12 hours.
RYNATAN Tablets: Adults — 1 or 2 tablets.
RYNATAN Pediatric Suspension: *Children over six years of age* — 5 to 10 mL (1 to 2 teaspoonfuls); *Children two to six years of age* — 2.5 to 5 mL (½ to 1 teaspoonful); *Children under two years of age* — Titrate dose individually

How Supplied RYNATAN® Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and 500 (NDC 0037-0713-96).

RYNATAN® Pediatric Suspension: pink with strawberry-currant flavor, in 4 fl. oz. bottles (NDC 0037-0715-67, labeled RYNATAN®-S*) and in pint bottles (NDC 0037-0715-68).

Storage: RYNATAN® Tablets — Store at room temperature; avoid excessive heat — above 40°C (104°F).

RYNATAN® Pediatric Suspension — Store at controlled room temperature — between 15°C–30°C (59°F–86°F); protect from freezing.

**Patent Pending*

RYNATAN®-S is the combination of RYNATAN Pediatric Suspension (4 fl. oz.) and a 10 mL calibrated, oral syringe.

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Facial Plastic News

WAYNE F. LARRABEE, MD, SECTION EDITOR
Virginia Mason Clinic, Seattle, Wash

Research Advances

This month's Facial Plastic News section reviews some of the advances in research presented at recent meetings of the American Association of Facial Plastic and Reconstructive Surgery. Surgeons are continually searching for mechanisms of enhancing the survival of flaps and grafts. Recent investigations have increased our understanding of some of the time-honored techniques that are used to reduce the risk of necrosis when transferring tissue from one site to another.

Surgical delay is used with large regional flaps when there is some threat of loss of viability of the distal portion of the flap. Calhoun et al (Department of Otolaryngology, University of Texas Medical Branch, Galveston) presented a description of the confusion in the surgical literature regarding the design of delayed flaps. They also presented a study comparing different designs of delay using a midline dorsal flap on white rats. The four surgical techniques included the following: Group 1 animals had an incision on all three sides with complete undermining of the flap. Group 2 animals were incised along the two long sides of the flap with no undermining. Group 3 animals were incised on all three sides and not undermined. Group 4 flaps were incised along the two long sides and completely undermined.

Postoperatively, tissue oxygen tension levels were measured in the distal portion of the flap using a transcutaneous oxygen monitor. On the eighth day, all flaps were raised entirely and replaced to the donor site. The results indicated that the bipedicle design (group 4) had significantly less necrosis than the other flaps, with the greatest amount of necrosis occurring in groups 2 and 3. Interestingly, the authors found an association between higher oxygen levels in the distal flaps and greater necrosis at 15 days.

The authors agree with the most widely accepted theory of the delay phenomenon, which is that delay enhances blood flow. They postulate that the increased blood flow is a result of a combination of inflammatory mediators at the flap site and a denervation surge of norepinephrine. The latter effect results subsequently in vasodilatation following norepinephrine depletion. This, in part, may explain the finding that the bipedicle design of flap delay yielded the best survival results.

Hyperbaric oxygen therapy has also been used to enhance the survival of flaps and grafts. One of its beneficial effects appears to be increased neovascularization. Willging et al, Chicago, Ill, presented a study of the effects of hyperbaric oxygen on composite graft survival. Their study involved white rabbits from which a block of skin and cartilage ($1\ cm^2$) from the margin of the ear was excised and replaced to the same site. Postoperative hyperbaric oxygen was administered daily. They found an increase in the number of complete grafts that survived the hyperbaric oxygen group when compared with a control group.

Goodman and Ruben (Department of Otolaryngology, University of California, Davis) looked at the effects of hyperbaric oxygen on irradiated skin flaps. A quantity of 25 Gy was administered to rats and a dorsal flap was elevated. Looking at different postoperative intervals, they found no significant effect on skin flap survival with the use of hyperbaric oxygen.

Another technique to enhance skin flap survival has been the use of cooling. Despite the risks of vasoconstriction and increased viscosity, some authors have felt that cooling reduces metabolic demand of the distal flap and can be a benefit to survival. Goding et al (Department of Otolaryngology, University of Minnesota, Minneapolis) looked at the effects of cooling on the survival of myocutaneous groin flaps in pigs. They were able to demonstrate a significant decrease in blood flow in the cooled flaps by dye fluorescence measurement. They found no deleterious effect from cooling the flaps and, in fact, noted that there was a delay in the onset of necrosis of the distal portion of the flap when compared with noncooled control flaps. They concluded that moderate cooling can be applied to a surgical flap with marginal vascularity without putting that tissue to increased risk of necrosis.

Constantino et al (Department of Otolaryngology, Northwestern University, Chicago, Ill) presented three papers on the evaluation of a new hydroxyapatite cement. The compound is tetracalcium phosphate, which can be mixed with water or blood and sets to solid hydroxyapatite. It can be used to fill bony defects and creates osteoid formation at the implant-bone interface. It appears to become integrated to underlying skull bone by osteoconduction. The authors reviewed the histologic findings, which showed a mild transient inflammatory response without foreign body reaction.

The implant was also used in the obliteration of cat frontal sinuses. There were no adverse reactions, infections, mucoceles, or implant extrusions. The implant did show gradual resorption with replacement by woven bone. The results of this study are very encouraging for the safe correction of dural defects in the absence of significant foreign body reaction.

Larrabee and coworkers (Seattle, Wash) presented a study of the effects of intralesional interferon gamma in patients with keloids and hypertrophic scars. Keloids and hypertrophic scars are both characterized by excessive collagen formation. Interferon gamma is a lymphokine that can down-regulate collagen synthesis in vitro and in vivo and, therefore, has potential therapeutic benefit in the management of abnormal scars. Intralesional scar injections of interferon gamma were performed to determine toxicity and to obtain evidence for the efficacy of this treatment. All scars treated decreased in linear dimensions and flattened out. Five of the 10 scars studied decreased at least 50% in linear dimensions. Interferon gamma can safely be administered intralesionally once per week up to a dosage of 0.05 mg for 10 weeks with no serious toxic effects. The most common reported side effect was a mild headache. A further blinded prospective study comparing interferon gamma with steroid injections is planned.—JAMES N. THOMPSON, MD, Winston-Salem, NC, and ROGER CRUMLEY, MD, Orange, Calif

The Punch in Skin Surgery

"Most of you are familiar with my work on hair transplantation using the punch, but I believe that many kinds of skin surgery are better treated with the punch than with other techniques," declared Norman Orentreich, MD, whose work in dermatologic surgery was honored with the Association of Facial Plastic and Reconstructive Surgery Distinguished Service Award at the Fifth International Symposium in Toronto, Canada.

The major advantage of the punch in skin surgery is the cosmetic correction it offers. For resolution of conditions such as ice pick scarring and leukoderma, it is the best technique currently available, according to Orentreich.

Documented as early as 1877, the punch instrument in its modern form was used by the German surgeon Kromeyer at the turn of the century. He is given credit for first using dental machines with rotating cylinders to remove hair from the face or to punch out ice pick scars.

"The punch is the perfect geometrical shape," said Orentreich. "You don't have to be a genius to cut a circle with a cylinder. It is very easy to cut surfaces with the punch because the minute the punch starts turning, it keeps cutting. It is also easy to judge the depth."

ICE PICK SCARS

For some people, ice pick scars are the bane of their existence. Explained Orentreich, "You'll get somebody with 50 little ice pick scars. You say to yourself, 'Dermabrasion isn't the answer. I'd have to go too deep or I'd have to do it so many times that I'd leave atrophy, telangiectasia, eczematization, and thin skin. How can I get a hole without planing it down?'"

The basic punch technique when used in the removal of ice pick scars is "no more difficult than electrolysis, once you learn how to do it," said Orentreich. The scar is punched out, removed, and replaced with a 50% larger graft taken from the donor site behind the ear. The excess tissue is removed from the plug, which is then placed in the recipient site. The graft is stabilized with pressure and taped in place. Orentreich cautioned to let the slightly elevated grafts alone for a full month or two. "They'll pop right out! Allow enough time for those grafts to grasp surrounding tissue."

Variations of the basic punch technique are used depending on the severity of the scarring. If the surface of the skin has little more than "dells," the scar simply can be punched out, allowed to elevate, and left to stop bleeding. In cases of severe acne, where passageways under the skin produce epithelium and cysts, the punch cylinder allows the surgeon to bore under the skin.

LEUKODERMA

Dermabrasion and burns sometimes produce localized loss of melanin in brown or black skin types. This resulting leukoderma easily can be resolved by using a 2-mm punch to "seed" the lightened areas with grafts from whole skin or epidermal tissue. The graft melanocytes send out tentaclelike pseudopods, which inject surrounding keratinocytes with melanosomes. "You get about a centimeter of pigment per punch. Using this method you can repigment an entire area—little by little it just closes up. The results are very good," said Orentreich.

OTHER USES

Of even greater importance, however, is the use of the punch technique to excise locally invasive epithelial tumors such as basal cell carcinomas. "In my hands, I find the punch for the tip of the nose is the optimal way to remove skin cancer," said Orentreich, adding that it permits the surgeon to sample deeply even to cartilage without removing uninvolved healthy tissue.

Orentreich recommended that, when working on the nose, donor tissue be taken from the back of the earlobe for the best tissue match. The bottom of the punch segment is trimmed so that it sticks up 1 to 2 mm to allow for shrinkage and, later, desiccation, dermabrasion, or shaving with a #10 blade. The graft is held in place with 6-0 sutures to ensure apposition and to keep the patient from dislodging the graft.—DEBORAH L. KALLGREN, Ijamsville, Md, in an interview with NORMAN ORENTREICH, MD, New York, NY

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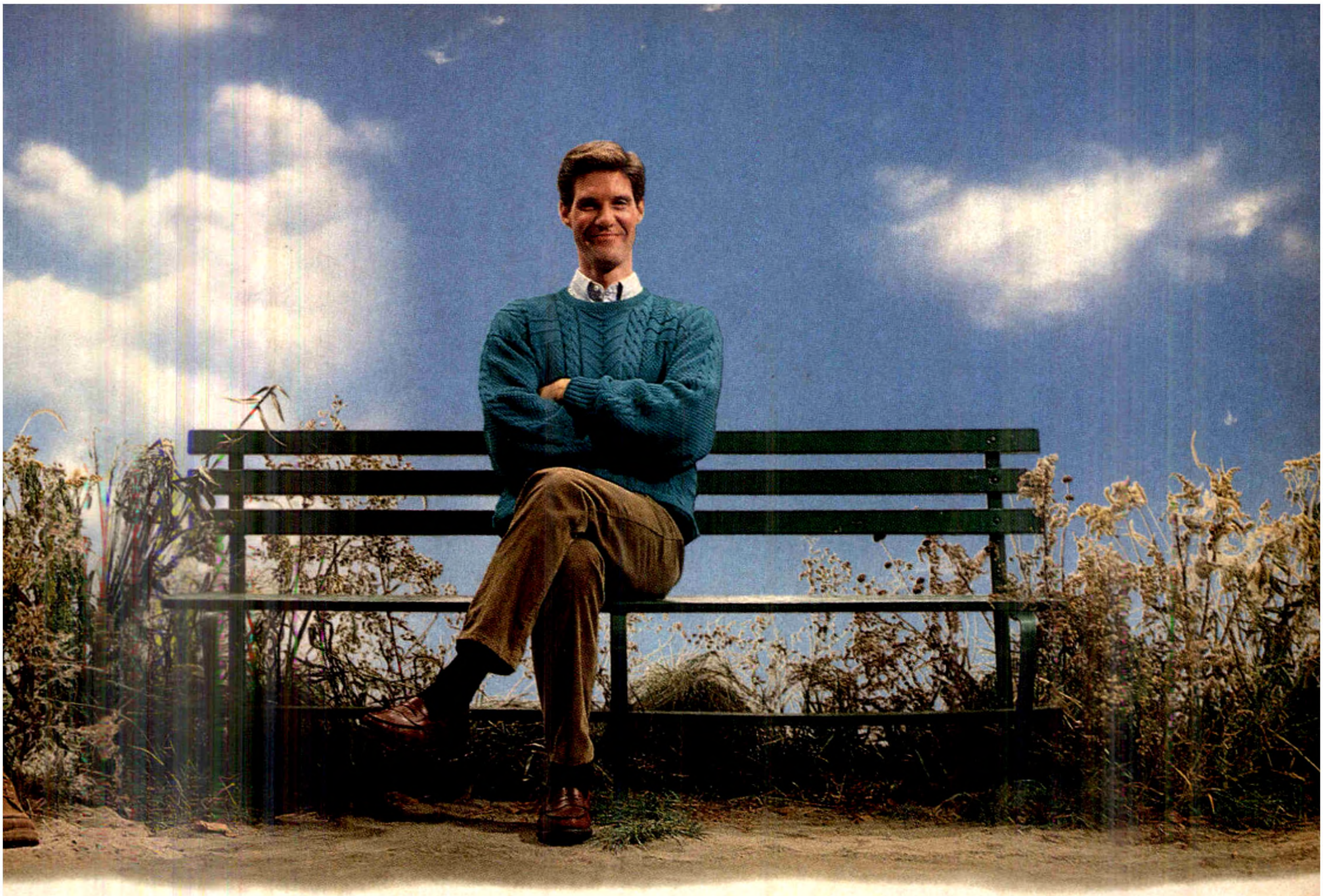

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(BECLOMETHASONE DIPROPIONATE, MONOHYDRATE)

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*In two out of four measures of nasal symptoms, $P < 0.01$.
†See WARNINGS and PRECAUTIONS in Brief Summary of Prescribing Information on next page. ‡Calculated on the dried basis.

Please consult Brief Summary of Prescribing Information on next page.

Beconase* Inhalation Aerosol
(beclomethasone dipropionate, USP)
For Nasal Inhalation Only

BRIEF SUMMARY

Beconase AQ* Nasal Spray, 0.042%*
(beclomethasone dipropionate, monohydrate)
***Calculated on the dried basis. For Intranasal Use Only.**

SHAKE WELL BEFORE USE.

The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase* Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ* Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2 1006 March 1989

REFERENCES: **1.** Kaliner MA. Pathogenesis of the late phase reaction and the mechanisms of action of corticosteroids in the treatment of allergic diseases. *N Engl Reg Allergy Proc.* 1986;7(3):1-5. **2.** Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol.* 1989;83(3):627-633. **3.** Salomonsson P, Gottberg L, Heilborn H, Norrlind K, Pegelow K-O. Efficacy of an oral antihistamine, astemizole, as compared to a nasal steroid spray in hay fever. *Allergy.* 1988;43(3):214-218. **4.** Beswick KBJ, Kenyon GS, Cherry JR. A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis. *Curr Med Res Opin.* 1985;9(8):560-567. **5.** Knight A, Kolin A. Long term efficacy and safety of beclomethasone dipropionate aerosol in perennial rhinitis. *Ann Allergy.* 1983;50(2):81-84.

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Transderm Scōp®
scopolamine
programmed delivery
0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

CIBA

Transderm Scōp®
scopolamine
(formerly Transderm-V)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS
Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS
Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS
General
Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients
Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions
Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C
Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use
Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS
The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE
Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION
Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION
Federal law prohibits dispensing without prescription.

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C88-5 (Rev. 2/88)

C I B A

References:
1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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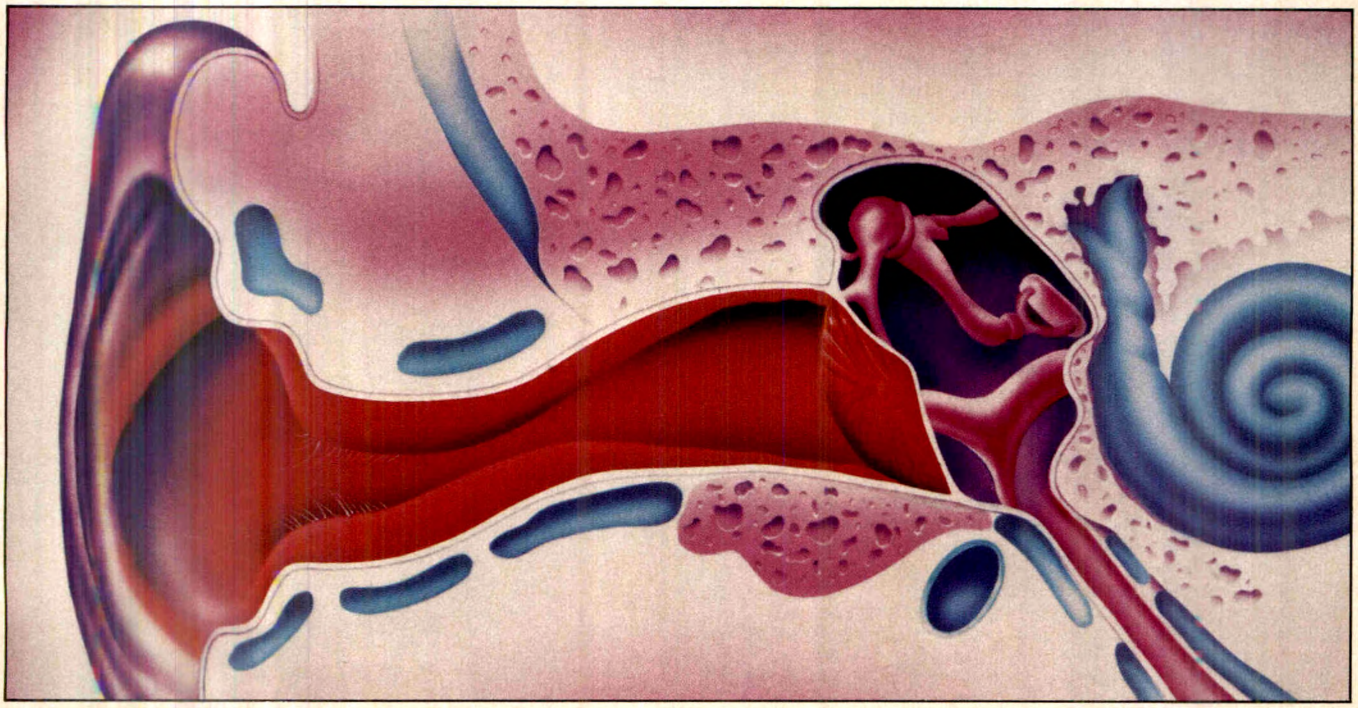

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References: **1.** Ordonez GE, Kime CE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: I. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-polymyxin B otic solutions. *Curr Ther Res.* 1978;23(May suppl):SS3-SS14. **2.** Kime CE, Ordonez GE, Updegraff WR, Glassman JM, Soyka JP. Effective treatment of acute, diffuse otitis externa: II. a controlled comparison of hydrocortisone-acetic acid, nonaqueous and hydrocortisone-neomycin-colistin otic solutions. *Curr Ther Res.* 1978;23(May suppl):SS15-SS28. **3.** Glassman JM, Pillar J, Soyka JP. Otitis externa: comparative *in vitro* sensitivities of clinical isolates of bacteria and fungi to nonantibiotic and antibiotic otic preparations. *Curr Ther Res.* 1978;23(May suppl):SS29-SS38.

VōSoL® HC
OTIC SOLUTION
(hydrocortisone and acetic acid otic solution, USP)

VōSoL®
OTIC SOLUTION
(acetic acid otic solution, USP)

Please see full prescribing information on next page.

Specify: Brand Medically Necessary, Dispense as Written

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VōSoL® HC

OTIC SOLUTION

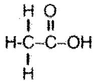
(hydrocortisone and acetic acid otic solution, USP)

VōSoL®

OTIC SOLUTION

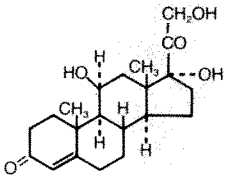
(acetic acid otic solution, USP)

Description: VōSoL (acetic acid otic solution, USP) is a solution of acetic acid (2%), in a propylene glycol vehicle containing propylene glycol diacetate (3%), benzethonium chloride (0.02%), and sodium acetate (0.015%).
VōSoL HC (hydrocortisone and acetic acid otic solution, USP) also contains hydrocortisone (1%) and citric acid (0.05%). The empirical formulas for acetic acid and hydrocortisone are CH_3COOH and $C_{21}H_{30}O_5$, with a molecular weight of 60.05 and 362.46, respectively. The structural formulas are:



$$\mathrm{H{-}\underset{H}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OH}$$

Acetic Acid



Chemically, hydrocortisone is:
Pregn-4-ene-3,20-dione,
11,17,21-trihydroxy-,(11β)-.

VōSoL and VōSoL HC are available as nonaqueous otic solutions buffered at pH 3 for use in the external ear canal.

Clinical Pharmacology: Acetic acid is anti-bacterial and anti-fungal; propylene glycol is hydrophilic and provides a low surface tension; benzethonium chloride is a surface active agent that promotes contact of the solution with tissues; hydrocortisone (in VōSoL HC) is anti-inflammatory, anti-allergic and anti-pruritic.

Indications and Usage: VōSoL — For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial.
VōSoL HC — For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation.

Contraindications: Hypersensitivity to any of the ingredients. VōSoL HC is contraindicated in vaccinia and varicella. Perforated tympanic membrane is considered a contraindication to the use of any medication in the external ear canal.

Warnings: Discontinue promptly if sensitization or irritation occurs.

Precautions: Transient stinging or burning may be noted occasionally when the solution is first instilled into the acutely inflamed ear.

Adverse Reactions: Stinging or burning may be noted occasionally; local irritation has occurred very rarely.

Dosage and Administration: Carefully remove all cerumen and debris to allow VōSoL to contact infected surfaces directly. To promote continuous contact, insert a wick saturated with VōSoL or VōSoL HC into the ear canal; the wick may also be saturated after insertion. Instruct the patient to keep the wick in for at least 24 hours and to keep it moist by adding 3 to 5 drops of VōSoL or VōSoL HC every 4 to 6 hours. The wick may be removed after 24 hours but the patient should continue to instill 5 drops of VōSoL 3 or 4 times daily thereafter, for as long as indicated.

How Supplied: VōSoL Otic Solution, in 15 mL (NDC 0037-3611-10) and 30 mL (NDC 0037-3611-30) measured-drop, safety-tip plastic bottles.
VōSoL HC Otic Solution, in 10 mL measured-drop, safety-tip plastic bottle (NDC 0037-3811-12).

Storage: Store at room temperature; avoid excessive heat. Keep container tightly closed. Rev. 5/89

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(ASTEMIZOLE) Tablets

THE FIRST ONCE-A-DAY ANTIHISTAMINE

OUTSTANDING SYMPTOM RELIEF

EFFICACY THAT LEAVES PATIENTS ALERT

Adverse effects seen with HISMANAL are generally mild and infrequent. 3.6% of patients noted weight gain; 0.7% with placebo.

Please see brief summary of prescribing information on next page.

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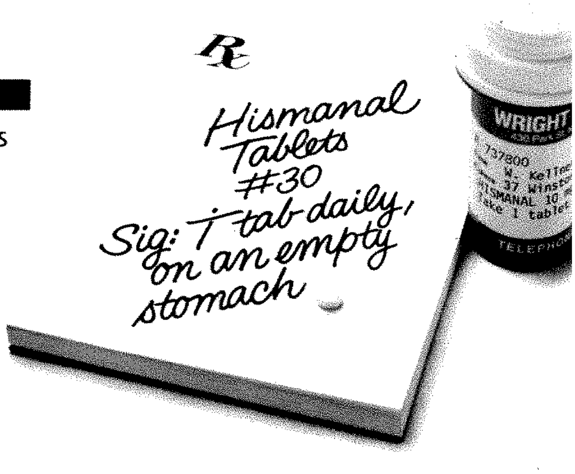
ONCE-A-DAY

HISMANAL®

(ASTEMIZOLE) Tablets

FOR PATIENT SATISFACTION



Before prescribing, please consult complete prescribing information of which the following is a brief summary.

DESCRIPTION

HISMANAL® (astemizole) is a histamine H_1-receptor antagonist available in scored white tablets for oral use.

CONTRAINDICATIONS

HISMANAL is contraindicated in patients with known hypersensitivity to astemizole or any of the inactive ingredients.

PRECAUTIONS

General: Caution should be given to potential anticholinergic (drying) effects in patients with lower airway diseases, including asthma.

Caution should be used in patients with cirrhosis or other liver diseases (See Clinical Pharmacology section).

HISMANAL does not appear to be dialyzable.

Caution should also be used when treating patients with renal impairment.

Information for Patients: Patients taking HISMANAL should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting HISMANAL therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby (see Pregnancy subsection). Patients should be instructed 1) to take HISMANAL only as needed, 2) not to exceed the prescribed dose, and 3) to take HISMANAL on an empty stomach, e.g., at least 2 hours after a meal. No additional food should be taken for at least 1 hour post-dosing. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic potential has not been revealed in rats given 260x the recommended human dose of astemizole for 24 months, or in mice given 400x the recommended human dose for 18 months. Micronucleus, dominant lethal, sister chromatid exchange and Ames tests of astemizole have not revealed mutagenic activity.

Impairment of fertility was not observed in male or female rats given 200x the recommended human dose.

Pregnancy: Pregnancy Category C: Teratogenic effects were not observed in rats administered 200x the recommended human dose or in rabbits given 200x the recommended human dose. Maternal toxicity was seen in rabbits administered 200x the recommended human dose. Embryocidal effects accompanied by maternal toxicity were observed at 100x the recommended human dose in rats. Embryotoxicity or maternal toxicity was not observed in rats or rabbits administered 50x the recommended human dose. There are no adequate and well controlled studies in pregnant women. HISMANAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Metabolites may remain in the body for as long as 4 months after the end of dosing, calculated on the basis of 6 times the terminal half-life (See Clinical Pharmacology section).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because certain drugs are known to be excreted in human milk, caution should be exercised when HISMANAL is administered to a nursing woman. HISMANAL is excreted in the milk of dogs.

Pediatric Use: Safety and efficacy in children under 12 years of age has not been demonstrated.

ADVERSE REACTIONS

The reported incidences of adverse reactions listed in the following table are derived from controlled clinical studies in adults. In these studies the usual maintenance dose of HISMANAL® (astemizole) was 10 mg once daily.

	Percent of Patients Reporting		
	Controlled Studies*		
ADVERSE EVENT	Hismanal (N = 1630) %	Placebo (N = 1109) %	Classical** (N = 304) %
Central Nervous System			
Drowsiness	7.1	6.4	22.0
Headache	6.7	9.2	3.3
Fatigue	4.2	1.6	11.8
Appetite increase	3.9	1.4	0.0
Weight increase	3.6	0.7	1.0
Nervousness	2.1	1.2	0.3
Dizzy	2.0	1.8	1.0
Gastrointestinal System			
Nausea	2.5	2.9	1.3
Diarrhea	1.8	2.0	0.7
Abdominal pain	1.4	1.2	0.7
Eye, Ear, Nose, and Throat			
Mouth dry	5.2	3.8	7.9
Pharyngitis	1.7	2.3	0.3
Conjunctivitis	1.2	1.2	0.7
Other			
Arthralgia	1.2	1.6	0.0

*Duration of treatment in Controlled Studies ranged from 7 to 182 Days

**Classical Drugs: Clemastine (N = 137); Chlorpheniramine (N = 100); Pheniramine Maleate (N = 47); d-Chlorpheniramine (N = 20)

Adverse reaction information has been obtained from more than 7500 patients in all clinical trials. Weight gain has been reported in 3.6% of astemizole treated patients involved in controlled studies, with an average treatment duration of 53 days. In 46 of the 59 patients for whom actual weight gain data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported in clinical trials or spontaneously from marketing experience with HISMANAL include: angioedema, bronchospasm, depression, edema, epistaxis, myalgia, palpitation, photosensitivity, pruritus, and rash.

Marketing experiences include isolated cases of convulsions. A causal relationship with HISMANAL has not been established.

OVERDOSAGE

In the event of overdosage, supportive measures including gastric lavage and emesis should be employed. Cases of overdose have been reported from foreign marketing experience. Although overdoses of up to 500 mg have been reported with no ill effects, cases of serious ventricular arrhythmias, including Torsades de pointes, following overdoses of greater than 200 mg have been reported. Patients should be carefully observed and ECG monitoring is recommended in cases of suspected overdose. An appropriate antiarrhythmic treatment may be needed. HISMANAL does not appear to be dialyzable.

Care should be taken not to exceed dosing recommended in the DOSAGE AND ADMINISTRATION section.

Oral LD_{50} values for HISMANAL were 2052 mg/kg in mice and 3154 mg/kg in rats. In neonatal rats, the oral LD_{50} was 905 mg/kg in males and 1235 mg/kg in females.

NDC 50458-510-01 (10 × 10 blister)   NDC 50458-510-10 (100 tablets)
Store tablets at room temperature (59°-86°F) (15°-30°C). Protect from moisture.

U.S. Patent 4,219,559 December 1988
JANSSEN PHARMACEUTICA INC., Piscataway, New Jersey 08854   1P41N98A-M

JANSSEN
PHARMACEUTICA

May, 1990

JPI-HS-063-1R

Somehow We Have To Stop the Train Wreck

Part 2

Last month, we reviewed the beliefs, conclusions, and problems that are looming large on the horizon of medicine and in our daily lives. We noted the powerful forces for change in our health care system (patients, government, and corporations) and drew the analogy of trains that appear to be speeding toward each other on a collision course. This month, we want to look into the future in the hope of anticipating problems and in search of possible solutions to avert the "train wreck."

Future Problems We Can Predict

Although prediction is far from an exact science, if one takes a close look at today's trends, projection of current events into the future is not a pretty sight in many areas. Major areas of concern for the future are the following.

1. Medicare reimbursement reform will advance, and we can expect further decreases in reimbursement.
2. The regulation of physicians will continue to increase and physician autonomy will decrease as all third-party payers try to reduce payments.
3. *Outpatient payment reform* will be the next focus for reducing funds from federal- and state-financed programs of health care.
4. Ambulatory care will continue to grow much faster than inpatient care, a process that will place further pressure on hospitals in terms of their financial survival.
5. Hospitals will find it necessary to specialize in relatively narrow areas of activity to survive as elements within health care networks, and many physicians and patients will commute between categorical units (with one hospital, for example, emphasizing diagnostic technology, another intensive care units, and still another cancer care).
6. Access to certain forms of care will decrease and rationing will increase. These phenomena will occur initially around high-cost, high-technology units and will gradually spread to other units.
7. Universal health care concepts will advance with support from groups like the Pepper commission as the government becomes convinced (by business and patients) that universal health care is affordable. New versions of the Massachusetts plan and the Canadian plan will be considered.
8. National health care costs will rise from $850 billion this year to $1.5 trillion in the year 2000 unless more effective measures to contain costs are developed.
9. Practice parameters and practice guidelines will proliferate and evolve into specific instructions for patient management.
10. The growth in our elderly population will mandate greater attention to the diseases of this population. The aging of the population of veterans covered under the Department of Veterans Affairs' health care system will push 11 million of these individuals out of the department's health care program and into the Medicare system over the next few years, with a major shift in funding between these two programs.
11. The trend to superspecialization will produce a gap between what physicians want to do and what the public needs. The present oversupply of specialists and shortage of generalists will increase in spite of policies designed to narrow the gap.
12. Various forms of credentialing (certification, recertification, fellowship certification, and added qualifications) will be the focus of significant debate. There will be new elements of physician sanctions for provision of questionable quality care, for impaired and dishonest physicians, and for incompetent physicians. Efforts to agree on a definition of *competence* in the practice of medicine will continue with regard to its measurement and validation, while various forms of certification and licensure are refined.

New Approaches and Solutions

Those who raise questions and challenge conditions should offer solutions to the problems they describe. I wish to propose 12 steps that deserve our attention because they represent partial solutions to some of the problems raised above.

These items are important elements in addressing problems in medicine and can be effective in stopping the impending train wreck about which we are all concerned.

1. We must focus our efforts on *caring* for patients and *convincing* them that we are the only group looking after their best interests.

2. The health care system must be reconfigured to promote health and disease prevention, rather than curing disease processes. Bernard Tresnowski, the president and chief executive officer of Blue Cross/Blue Shield, Chicago, Ill, has emphasized that this is the *most important single solution* to the present crisis.

3. Health care facilities must be reorganized into a logical system with greater efficiency and tighter fiscal management. The old pattern of competing, mirror-image hospitals within a community is no longer affordable in many localities.

4. Brokers, corporate health care providers, and investment bankers must be encouraged to find interesting careers away from the health care field. Their goals, methods, and profits are usually not consistent with the best interests of patients.

5. A greater spirit of volunteerism, charity, and humanitarianism must be fostered at all levels within the health care system. Physicians are the logical individuals to provide the leadership along this path.

6. Support groups, home health care programs, and hospice facilities are examples of networks and informal groups that must be strengthened so that they can replace more expensive medical facilities whenever appropriate. This can often be done with an enhanced element of caring without sacrificing the quality of care provided.

7. We must support the growth of medical information systems as integral resources for medical communication and decision making.

8. Medical education must evolve into a system with greater emphasis on curriculum relevance and the rewarding of good teachers. We should organize our educational resources into a system in which slightly different missions are assigned to medical education centers, based on their inherent strengths and weaknesses.

9. We must demand fair media coverage of physicians and we must caution those who repeatedly broadcast and print material that leads to unrealistically high public expectations for medical miracles at every turn.

10. We must form coalitions and alliances with the public (our patients) at every opportunity so that together we may lobby for *increased patient access* to a system of *personalized* and *high-quality medicine* provided at a *fair cost.*

11. We must develop better strategies at every level to achieve damage control. We have already taken a number of hits, and more torpedoes are in the water. The manner in which we deal with the current crisis during the next 3 years will be important, but we must not let immediate events shape our long-range plan.

12. We must clean up our own house. It is no longer reasonable to assume that there are only one or two bad apples in the barrel. We have to accept the fact that 5% to 10% of physicians need help in regard to one or more serious problems related to their professional ability, level of knowledge, health, substance abuse, or sociopathic/unethical behavior.

The reason we physicians are watching events slip away from us is that we have been neutralized, now that the game has become patients, government, and business ganging up on physicians. We are being asked to provide greater access, higher quality, and lower cost *simultaneously* to a growing number of patients with a medical environment of expensive technology. Our national medical ethic has been the preservation of life at all cost and avoidance of placing a dollar value on such ephemeral items as a child's hearing or vision, an elderly person's long-term convalescence, or a premature neonate's survival.

But now that ethic is being challenged by auditors and accountants, and their message is clear—keep one eye on the *care* and the other eye on the *cost.* At the present time, ethical principles have been pushed aside by the force of financial pressures, because the exercise is not driven by health *policy* issues but by *budgetary* issues. The problem is that we have been running the country on borrowed money and the hope of a growing economy that will pay the bill. When, and if, the economy falters or turns down and government revenues decrease, our budget *problem* will become a budget *crisis,* with a need for major cuts in health care spending and with the inevitable rationing of health care as one of the key steps in dealing with the crisis.

The only viable strategy for dealing with these issues is to educate the public in life-styles that will reduce spending in major health care categories and to rebuild our alliance with patients on behalf of the funding of a realistic, affordable, accessible, high-quality health care system. That is the goal and that is the challenge.

Each of us has the potential, one patient at a time, to educate the public regarding these issues and, in so doing, to stop the train wreck. If we fail in that responsibility, future generations of physicians will not enjoy the freedom and the excitement of medicine as it is currently practiced.

Byron J. Bailey, MD
Chief Editor

Expedited Publication

Prevention of Microvascular Thrombosis With Controlled-Release Transmural Heparin

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• The use of controlled local-release heparin was studied as a means to prevent thrombosis in microvascular surgery, using a rat arterial inversion graft as a model. Polyvinyl alcohol embedded with heparin was placed around the outside of inversion graft anastomoses in 16 animals. Results were compared with control group animals in which polyvinyl alcohol alone was placed around the graft or systemic heparin was given. Vessel patency rates were significantly higher for animals receiving either systemic or transmural heparin than for animals in the control group. Controlled local delivery of heparin did not cause measurable systemic anticoagulation. However, the complication of local hematoma formation occurred as frequently as in the systemic heparin group. Controlled transmural release of heparin has an effective local antithrombotic effect and may hold promise for use in clinical practice.

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In spite of the emphasis on surgical detail in microvascular surgery, surveys of clinicians reveal a persistent thrombosis rate of approximately 10%.[1-4] Many systemic pharmaceutical agents, including heparin, aspirin, dextrans, dipyridamole, and prostacyclins, have been used to help maintain or improve the patency of microvascular anastomoses.[5-9]

Heparin has been extensively investigated and new pharmacological effects continue to be found.[9-17] Heparin's primary mode of action is the inactivation of thrombin via the acceleration of anti-thrombin III activity. It binds to anti-thrombin III, accelerating the stoichiometric reaction between thrombin and anti-thrombin III, thereby inactivating thrombin. Heparin also inactivates other factors, particularly factor Xa; this occurs at concentrations considerably lower than those required to inactivate thrombin. Additionally, heparin appears to prevent the deposition and aggregation of platelets on damaged endothelium or exposed subendothelial tissue.[18] Heparin also inhibits smooth-muscle proliferation after endothelial injury by a mechanism that seems to be independent of its anticoagulant effect.[15] Researchers have postulated that this trauma-induced smooth-muscle proliferation and subsequent vessel wall thickening may contribute to delayed stenosis at anastomotic sites.

When used systemically, heparin is effective in preventing microvascular thrombosis; however, its systemic effects are associated with significant morbidity and even mortality.[5,19] Reported complication rates range from 5% to 33% and include substantial problems such as intracerebral hemorrhage, gastrointestinal bleeding, and surgical wound hematoma.[18,20] Wound hematomas can induce microvascular thrombosis by means of external vessel compression and by inducing spasm in the vessel wall musculature. In the opinion of most surgeons, any potential advantages of

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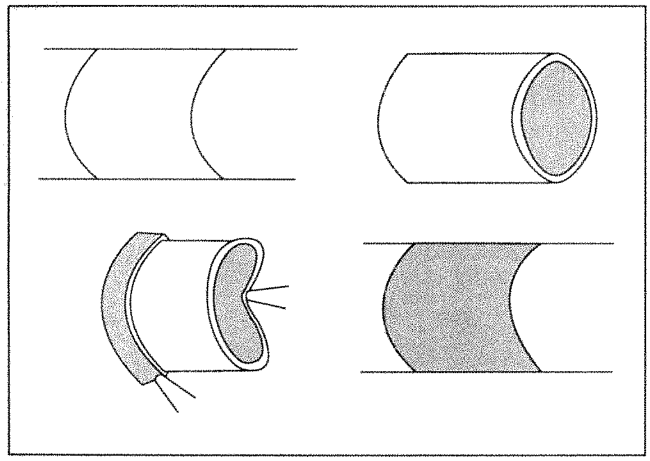

Fig 1.—Diagram of arterial inversion graft. After inversion and reanastomosis, the former adventitial surface lines the inside surface of the vessel.

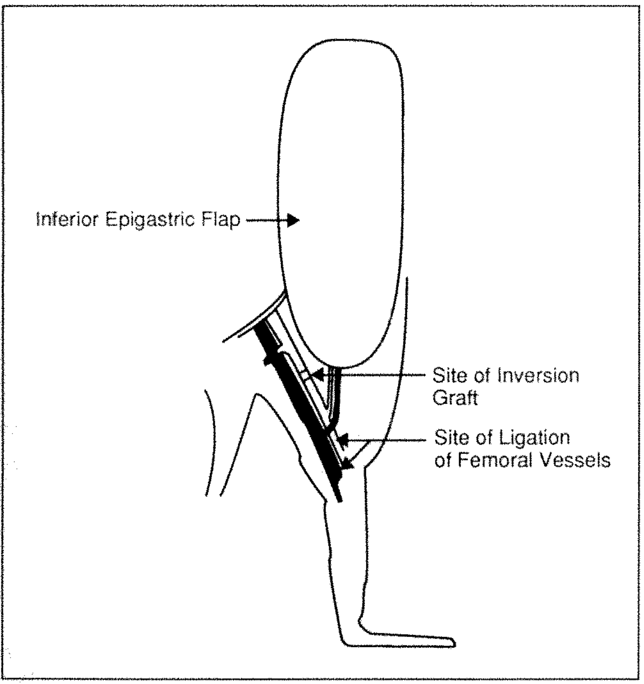

Fig 3.—Sketch of skin flap based on inferior epigastric vessels. Arterial inversion graft is proximal to inferior epigastric artery take-off. Ligation of distal femoral artery precludes the possiblity of collateral inflow.

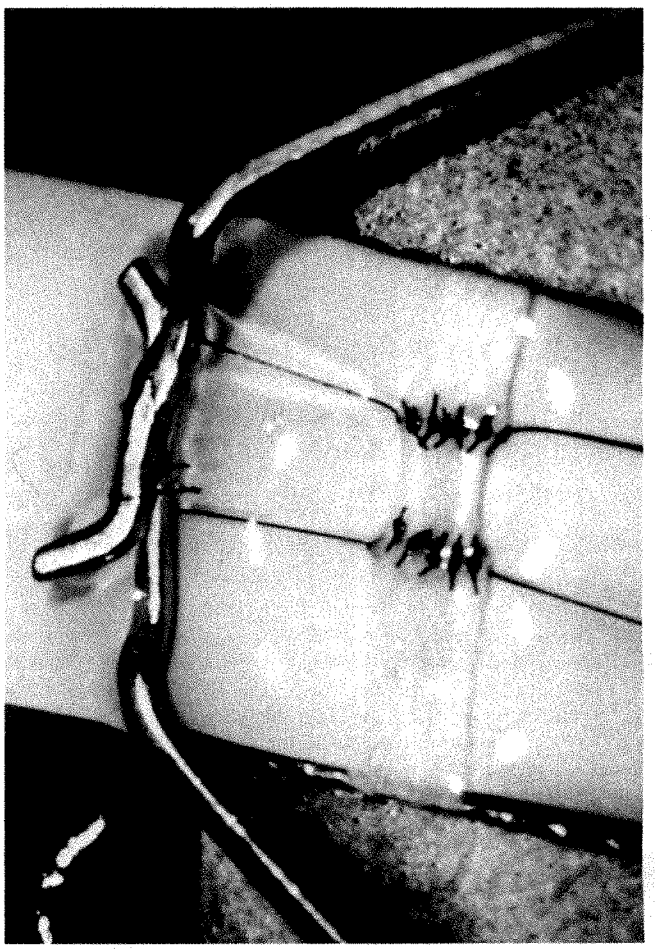

Fig 2.—Photomicrograph of rat femoral artery inversion graft (×10) immediately following reanastomosis, prior to opening of frame clip clamps.

routine systemic heparin are clearly offset by the possibilities of adverse local and distant complications.

While most microvascular surgeons do not use systemic heparin routinely, local irrigation with heparin has been shown to be useful. Its use in clinical practice, in fact, is nearly universal.[21] Complications from local irrigation are virtually nonexistent. This led us to consider the possibility that a more prolonged local effect, if achievable, would be a potentially significant improvement over simple intraoperative irrigation. Local, transmural delivery of heparin released in a controlled fashion from a substance placed around the outside of the vessel wall immediately following the anastomosis seemed an intriguing concept. The benefits of systemic heparin might be achieved without assuming any of the risks of systemic use.

Recently, such a method has been devised for the local release of heparin from polyvinyl alcohol (PVA).[17] Polyvinyl alcohol is a nontoxic polymer that has previously been used in humans for blood volume expansion. Polyvinyl alcohol is water soluble, produces minimal tissue inflammation, and has well-characterized release kinetics.[22,23]

In a rat model where endothelial damage was produced in the common carotid artery, local transmural release of heparin in PVA was found to have a very significant local antithrombotic effect and did not cause systemic anticoagulation. Although heparin is a fairly large macromolecule, radiolabeled heparin was found throughout cells in the vessel wall within hours after being applied.[24] It remained in high concentration for 24 to 48 hours.[24] Since thrombosis in microvascular anastomoses usually occurs within the first hour, these observed kinetics of release and subsequent diffusion with active uptake would seem to be appropriate for prophylactic use in microvascular surgery.[25,26] Controlled-release and transmural delivery of periadventitial heparin has further been shown to reduce myointimal proliferation, again without causing measurable systemic anticoagulation.[27]

An arterial inversion graft is a useful model for studying pharmacological methods of preventing microvascular thrombosis because it is analogous to clinical situations where strands of adventitia may be incorporated into the anastomosis or where intimal damage exposes subendothelial collagen. The inversion graft, previously described in the rabbit, replaces normal endothelium with adventitia containing type III collagen (Fig 1). In this model, systemic heparin has already been shown to increase patency rates significantly.[9]

The purpose of our study was to investigate the efficacy of transmural delivery of controlled local-release heparin in maintaining patency of a thrombogenic microvascular inversion graft in the rat femoral artery.

MATERIALS AND METHODS

Technique

Sprague-Dawley rats (350 to 400 g) were anesthetized with intraperitoneal Equithesin (each milliliter contains chloral hydrate, 0.042 g; phenobarbital, 0.0097 g; and magnesium sulfate, 0.021 g) (3 mL/kg), followed by 0.1- to 0.2-mL increments for the duration of the procedure. The groin and abdomen were shaved and remaining hair was removed with a depilatory agent. Body temperatures were maintained with a warming pad.

An inversion graft of the femoral artery was fashioned as follows: adventitia was thoroughly removed from the proximal femoral artery, a microvascular clamp was applied, and a segment of artery equal in length to the vessel diameter was inverted and anastomosed with a 10-0 nylon suture on a 75-μm needle (nine stitches per anastomosis [Fig 2]). A graft of this length gave reproducible thrombosis, and alteration of the length of the graft altered the degree of thrombogenicity. This method was tested and calibrated on 30 rats.

Table 1.—Study Design*

Group	N	Graft	Heparin	Mean PTT, s
A	16	Noninverted	None	22.0
B	16	Inverted	Systemic	71.1
C	16	Inverted	None (PVA only)	22.5
D	16	Inverted	Controlled release	23.8

*PVA indicates polyvinyl chloride; PTT, partial thromboplastin time.

Table 2.—Vessel Patency

Group	1 h	4 h	24 h	96 h	Total
A	4 patent	4 patent	4 patent	3 patent; 1 thrombosed	15 patent (94%); 1 thrombosed
B	3 patent; 1 40% occluded	3 patent; 1 40% occluded	3 patent; 1 thrombosed	2 patent; 2 thrombosed	11 patent (69%); 3 thrombosed; 2 40% occluded
C	4 thrombosed	4 thrombosed	1 patent; 3 thrombosed	4 thrombosed	1 patent (6%); 15 thrombosed
D	3 patent; 1 thrombosed	3 patent; 1 thrombosed	2 patent; 1 thrombosed; 1 40% occluded	3 patent; 1 thrombosed	11 patent (69%); 4 thrombosed; 1 40% occluded

Table 3.—Flap Survival

Group	1 h (n = 16)	4 h (n = 12)	24 h (n = 8)	96 h (n = 4)
A	16 viable	12 viable	8 viable	3 viable; 1 70% necrotic
B	16 viable	12 viable	2 viable; 3 30% mottling; 3 30% necrotic	1 viable; 1 30% necrotic; 2 total necrosis
C	16 viable	12 viable	7 viable; 1 10% necrotic	3 necrotic; 1 10% necrotic
D	16 viable	12 viable	5 viable; 2 30%-40% mottled; 1 10% necrotic	2 viable; 1 10% necrotic; 1 total necrosis

A 6 × 4-cm flap based on the inferior epigastric artery was raised, and the femoral artery was ligated distally, thus making the flap's viability dependent on the patency of the arterial inversion graft (Fig 3). In all animals, less than 1.0 mL each of 1% lidocaine hydrochloride (to reverse arterial spasm) and 1:10 000 heparin was used for irrigation of the surgical site.

Study Design

Sixty-four rats were studied in four groups (Table 1). In group A the anastomoses were performed as described, except that the segment of artery was *not* inverted. This group was included to verify that removal and replacement of a short segment of vessel was in and of itself not particularly thrombogenic, and could be accomplished reliably and repeatedly. Animals in *all* the remaining groups had inverted grafts.

Animals in group B were anticoagulated with a single dose of systemic heparin (400 U/kg subcutaneously) immediately after induction of anesthesia. Assignment of animals to the remaining two groups (groups C and D), was done randomly on completion of the arterial inversion graft, after any oozing had stopped. In group C, a Silastic shell (Silicone A, Dow Corning Corp, Midland, Mich) with a capacity of 0.06 mL was placed around the anastomosis and filled with PVA as a viscous gel (Elvax, DuPont Corp, Wilmington, Del, 16% weight to volume in water). In group D, 0.02 mL of heparin (10 000 U/mL) and 0.04 mL of PVA were mixed and placed in the Silastic shell. The total amount of heparin in the shell, therefore, was approximately 200 U. By comparison, the average intravenous dose in group B animals was approximately 150 U.

One hour after the procedure, blood was taken for measurement of partial thromboplastin times (0.1 mL of 3.2% sodium citrate per 1 mL of blood). This was done to quantify the degree of systemic anticoagulation in group B animals, and to verify that the local release of heparin in group D animals did not cause systemic measurable anticoagulation.

Four animals (25%) in each group were killed at each of the following intervals: 1 hour, 4 hours, 24 hours, and 4 days. Assignment to these various intervals was done randomly prior to surgery.

Quantification

The appearance of the inferior epigastric artery flap was assessed in surviving animals at 4 hours, 24 hours, and 4 days postoperatively. Observations were made separately by two individuals who were unaware of the animal's group assignment. Capillary filling, skin color, and the area of any flap necrosis were recorded.

Vessel patency was examined when the animals were killed. Rats were anesthetized, then perfused and fixed with intracardiac 0.1-mol/L phosphate-buffered saline at physiologic pressure (pH, 7.4; mean pressure, 80 mm Hg) followed by 4% paraformaldehyde. During perfusion, the femoral artery was cut distal to the anastomosis and patency was evaluated without any milking or manipulation of the anastomosis. The degree of free flow of perfusate was graded by gross observation (none, poor, fair, good, and excellent). Vessels were then studied by light microscopy (hematoxylin-eosin–stained 5- to 8-μm sections) to quantify the cross-sectional area occluded by thrombus. This was measured at the most stenotic point, as determined by serial sections taken along the length of the inversion graft. The area of the lumen remaining patent was measured using light microscopy with a reticule and compared with the area enclosed by the external elastic lamina, now on the inside of the vessel. The majority of vessels were either totally occluded or patent. However three vessels showed partial occlusion (Table 2).

Morphologic Studies

To further study some of the important morphologic criteria not assessable on light microscopy, a parallel study of additional animals was done to allow preparation of vessels for study by electron microscopy and immunocytochemical staining. These animals are not included in the tabular displays nor are they included in the statistical analyses. Due to differences in the techniques required for histologic preparation (such as longitudinal vs transverse sectioning), it was not possible to assess patency accurately in these animals.

Two vessels representative of each group were studied by scanning electron microscopy at intervals of 1 hour, 24 hours, and 4 days after surgery. For this, a perfusate of 2.5% glutaraldehyde and 2% paraformaldehyde was substituted. The vessel was cut longitudinally, mounted, placed in buffered saline followed by 1% osmium tetroxide, dehydrated in graded ethanols, critical-point dried, coated with gold, and examined by scanning electron microscopy (Phillips, Eindhoven, the Netherlands).

In addition, inversion grafts from four animals killed 4 days postoperatively, one representing each group, were embedded in epoxy resin (Polybed) for transmission electron microscopy. Inversion graft segments from yet another five animals, killed at various intervals, were fixed in methycarnate and immunocytochemically stained to identify fibrinogen or fibrin using a primary rabbit antiserum with avidin-biotin complex/horseradish peroxidase and a diaminobenzidine substrate using nickel dichloride to blacken.

RESULTS

Vessel Patency

Gross estimation of flow from the cut femoral artery distal to the inversion graft during perfusion gave results consistent with the quantitative data obtained by measuring the cross-sectional area from tissue sections. Patency was essentially an all-or-none phenomenon with only three vessels showing partial occlusion by thrombus (Table 2).

Untreated inversion graft controls (group C) were consistently occluded (6% patency rate), while noninverted controls (group A) were consistently open (94% patency rate). There was no difference (69% patency rate each) between the systemic heparin (group B) and PVA-heparin animals (group D). Inverted grafts treated with systemic heparin or PVA-heparin remained patent significantly more frequently than did grafts in the untreated control group (69% vs 6% patency rates, $P < .05$ by χ^2 test).

Flap Survival

All flaps examined less than 24 hours postoperatively appeared viable. Visual assessment of flap viability did not correlate with vessel patency, and, occasionally, large areas of a flap appeared viable when the vessels were occluded (Table 3). Conversely, on occasion flaps were partially necrotic even when the artery was unequivocally patent. This was presumably due to either infection or relative venous insufficiency caused by hematoma compression.

Electron Microscopy

The differences 1 hour postoperatively between inverted and noninverted grafts observed by scanning electron microscopy are shown in Fig 4. The irregular surface lining the lumen of the inverted graft is readily apparent. In the untreated inverted control group, scanning electron microscopic views were not obtainable at this 1-hour interval because, after several minutes, the graft was always occluded. Inversion grafts treated with either systemic or transmural heparin showed a "pseudoendothelium" by day 4. Figure 5 shows the surface at 4 days postoperatively of such an inverted graft treated at surgery with transmural heparin. Flattened, thin cells can be identified stretching across the collagen and other adventitial tissues forming a neointima. Morphologic characteristics observed on transmission electron microscopy verified that these cells stretched over this pseudointima were platelets (Fig 6).

Immunocytochemistry

Immunocytochemical staining of untreated inverted vessels, harvested 1 hour postoperatively, demonstrated the presence of fibrinogen and fibrin in the thrombus (Fig 7). In obvious contrast, neither fibrinogen nor fibrin was identified on the surface of vessel lumina treated with either systemic or transmural heparin.

Coagulation Studies

Partial thromboplastin times measured on samples drawn 1 hour after completion of the procedure (Table 1) showed no measurable systemic effect of heparin in the controlled-release transmural heparin group (partial thromboplastin time, 23.8 seconds; control time, 22.0 seconds). Animals in the systemic heparin group had a mean partial thromboplastin time just over three times the control level (partial thromboplastin time, 71.1 seconds).

Complications

Twelve inversion grafts were found to be thrombosed immediately on removal of the vessel clamps and were,

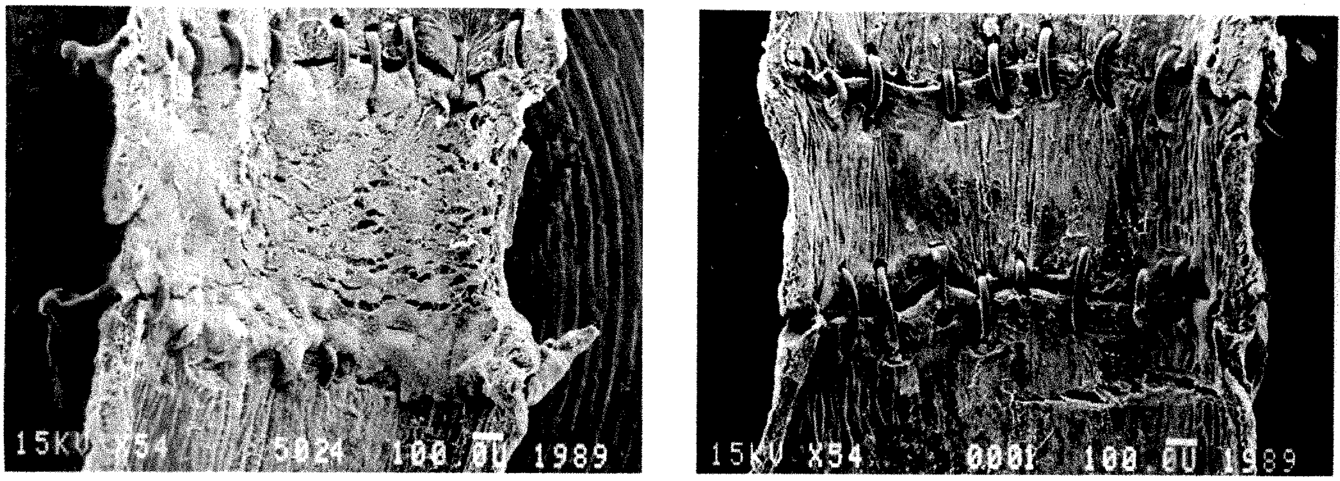

Fig 4.—Left, Scanning electron photomicrograph (×54) of rat femoral artery inversion graft 1 hour postoperatively (group D). Right, Scanning electron photomicrograph (×54) of noninverted rat femoral artery graft 1 hour postoperatively for comparison (group A).

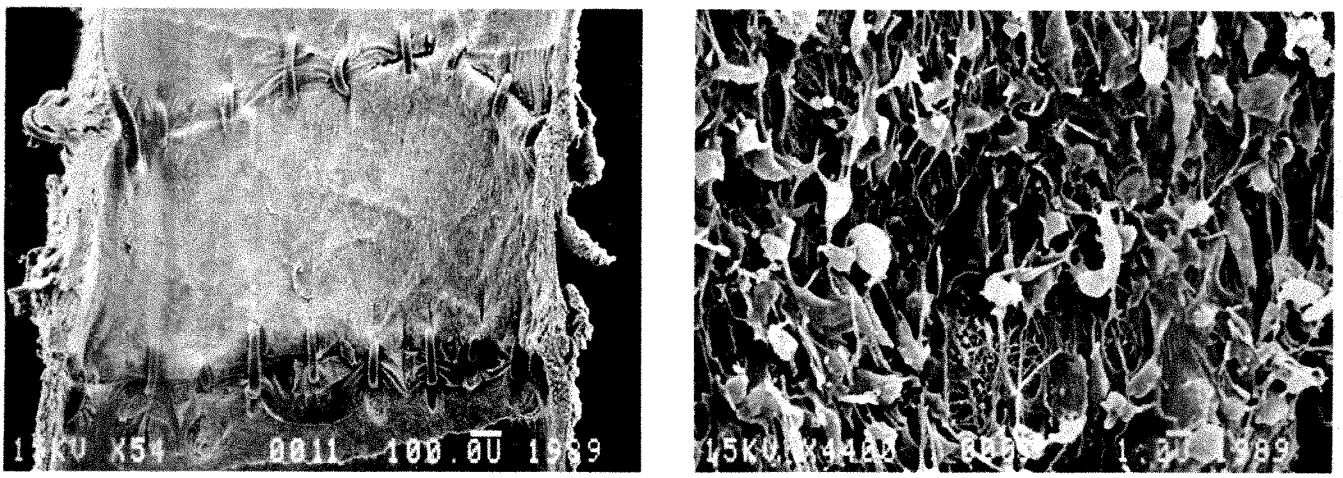

Fig 5.—Left, Scanning electron photomicrograph (×54) of rat femoral artery inversion graft treated with controlled-release heparin (group D) 4 days postoperatively. Note smooth graft surface. Vessel was fully patent at time of perfusion. Right, Higher magnification (×4400) of graft shown at left. Flattened cells seen forming neointima.

therefore, excluded entirely from the study. These were equally distributed among groups B, C, and D (four in each group). Histologic examination of these grafts invariably showed that adventitia on the back wall had been caught up in a suture. They were excluded on the grounds that the model was not technically accomplished in these animals and that they could not provide a meaningful comparison. Five other rats died of *Mycoplasma* pneumonia and were also excluded. Again, they were equally distributed among all four groups. Replacement animals were entered into the study for each of those excluded.

Eleven rats developed significant, but not compressive, hematomas around the anastomoses as follows: 6 in the transmural heparin group, 4 in the systemic heparin group, and 1 in the untreated control group (Table 4).

COMMENT

The use of systemic heparin has previously been shown to be effective in maintaining microvascular patency. However, as already mentioned, it is not used routinely in clinical practice because of the prohibitively high local and systemic complication rates associated with its use.

This study demonstrates that transmural delivery of heparin is as effective as systemic heparin therapy in maintaining microvascular patency in an exceedingly thrombogenic model. Importantly, controlled local release of heparin did not cause measurable systemic anticoagulation. Our initial goal of achieving a significant local effect without causing discernible systemic effects seems to be realizable.

The total amount of heparin used in the transmural delivery system was somewhat more than the amount used for one-dose systemic therapy. Since it was released gradually over a period of several days, it did not accumulate in the bloodstream to any significant extent. Release of large molecules, such

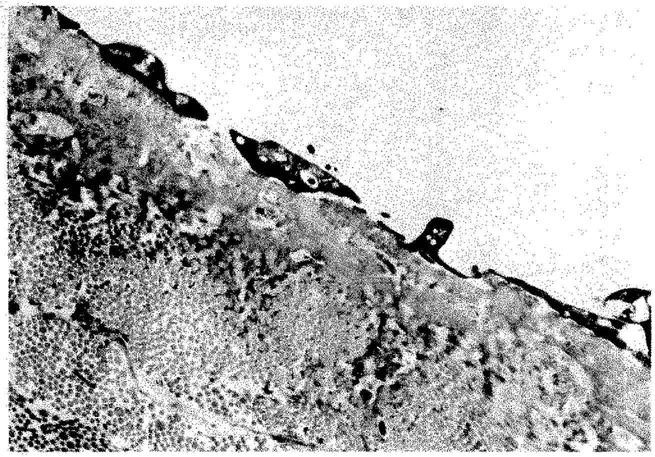

Fig 6.—Transmission electron photomicrograph (×3600) of controlled-release heparin-treated inversion graft 4 days postoperatively providing verification that cells forming neointima are platelets.

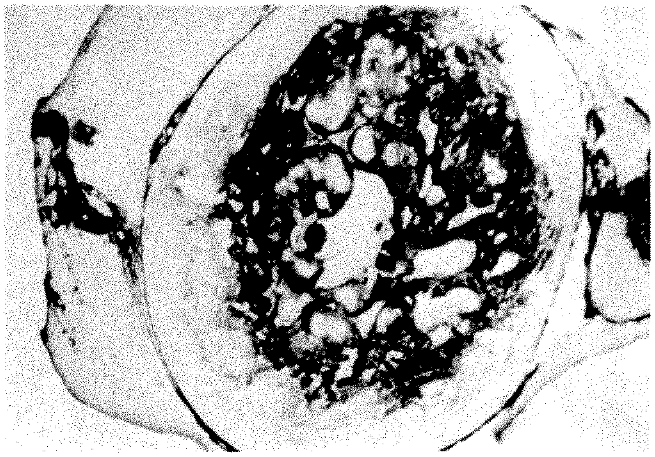

Fig 7.—Photomicrograph (×100) of thrombosed arterial inversion graft, untreated (group C), 1 hour postoperatively. Immunocytochemical staining (dark areas) demonstrates that thrombus is composed of fibrin and fibrinogen rather than platelets.

as heparin from delivery systems such as PVA, follows roughly predictable kinetics. The amount of drug released is high initially and decreases rapidly over several days. Once released from the polymer, the heparin macromolecules diffuse toward, and then across, the vessel wall. Passage across the vessel wall presumably also involves active transport mechanisms. The proportion of drug that remains bound to the vessel wall locally vs the amount that is released into the general circulation is also not yet known.

As discussed in the introduction of this article, the acute effects of heparin are basically directed toward prevention of a thrombus, rather than lysis of clots. The precise cause of local hematoma formation associated with transmural heparin delivery is not certain. The Silastic shell and the PVA with heparin were not applied until all oozing had ceased. In placing the Silastic shell, the anastomosis may have been disturbed and minor oozing may have resumed. Periadventitial heparin may have prolonged this oozing, eventually leading to formation of a significant hematoma. Alternatively, while heparin has no known fibrinolytic activity, it may stimulate the release of tissue-plasminogen activator, which would perpetuate any minor anastomotic leaks.[13] Equally plausible is the possibility that heparin diffused outside the Silastic shell and perpetuated bleeding from tissues in the surgical wound.

Table 4.—Complications

Group	Hematoma Rate (%)
A	0/16 (0)
B	4/16 (25)
C	1/16 (6.25)
D	6/16 (37.5)

A lower dose of heparin delivered transmurally could have an equally antithrombogenic effect without causing hematoma formation. The model used here is so much more thrombogenic than the occasional less-than-perfect clinical anastomosis that a lower dose of transmural heparin would almost certainly be effective in a clinical setting. Alternatively, a polymer with a higher viscosity might hinder oozing and be associated with a lower hematoma rate. It is unlikely that a more tightly fitting shell could be designed without introducing the possibility of kinking or compressing the vessel wall. This could restrict flow and itself become a cause of thrombosis.

While surgical technique is certainly the most important factor in the success of microvascular surgery, transmural heparin may eventually have a place in maintaining the patency of microvascular anastomoses in the clinical milieu. In this extremely thrombogenic model, transmural heparin reduced thrombosis rates from 94% to 31%. If controlled release and transmural delivery of heparin in humans could achieve a similar decrease in clinical thrombosis rates, without the systemic effects of currently available pharmacologic interventions, it would be a valuable tool.

Certainly clinical studies of controlled-release heparin for microvascular surgery will be worth undertaking at some point. Studies using venous models are considerably more difficult to perfect and work with but would be more analogous to the clinical situations where venous thrombosis predominates over arterial thrombosis. We will need to verify that transmural delivery is effective in a venous model. Future laboratory work will also be needed to study the precise kinetics of controlled-release and transmural delivery of heparin and to determine a minimally efficacious dose. Research using other polymer delivery systems or other antithrombotic drugs may also be fruitful.

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Management of the Paralyzed Lower Eyelid by Implanting Auricular Cartilage

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• The success of a procedure to reanimate paralyzed eyelids is determined by the functional and cosmetic results. When the cornea is covered during blinking and sleeping, function has been restored, while a pleasing cosmetic result has been achieved if the eyes appear symmetrical when the lids are open. Several procedures have been developed to restore closure of the paralyzed upper eyelid (implantation of gold weights or open wire springs) or to correct lower lid lagophthalmos and ectropion (lower lid tightening with a Bick procedure or insertion of a closed eyelid spring). In some cases, even a combination of the Bick procedure and insertion of a spring may be insufficient to correct lower lid droop; therefore, we developed a technique to place cartilage into the lower eyelid to correct lid droop. The procedure, suggested by one of us (D.B.S.), has been performed on 51 patients to date. This article reviews our experience with these 51 consecutive patients.

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Techniques to restore facial function and cosmesis in patients with facial paralysis are evolving. Multiple procedures may be needed to reanimate various regions of the face, but closure of the eyelids is of paramount importance because eyelid function is essential to protect the cornea. The technique we developed to implant auricular cartilage into the lower eyelid is reproducible as well as reversible, and improves the position of the lower lid as well as restoring function and appearance.

PATIENTS AND METHODS

Indications for Cartilage Insertion

Auricular cartilage was inserted in patients with facial paralysis in whom significant lower eyelid lagophthalmos and/or ectropion was present (Fig 1). Patients underwent lower eyelid procedures both to improve cosmetic appearance and to improve coverage of the lower portion of the cornea. In addition, a lower lid tightening procedure (Bick)[1] was often performed at the same time the cartilage was implanted.

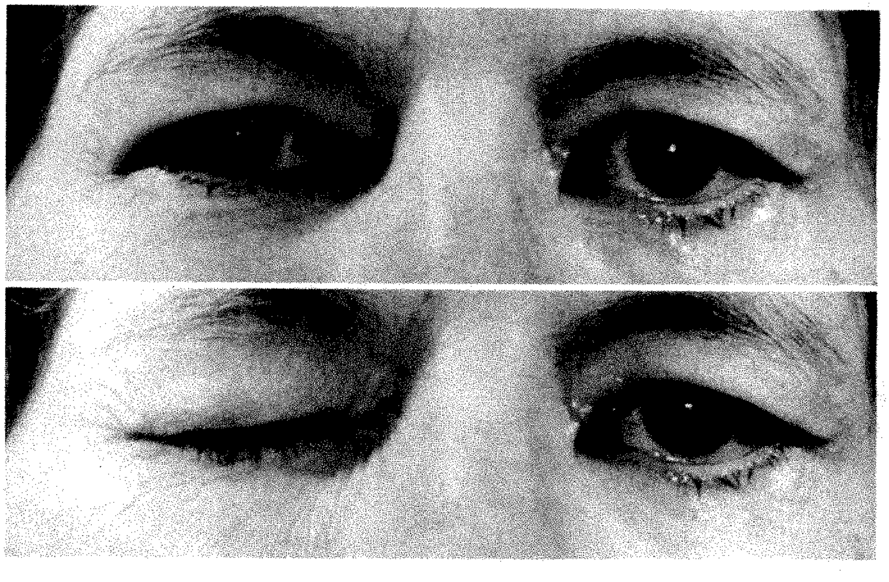
The causes of facial paralysis requiring lower eyelid reanimation are summarized in the Table. These patients usually had their upper eyelids reanimated with a gold weight[1] or open wire spring.[2]

Cartilage Insertion Technique

Lower eyelid reanimation with cartilage is performed under local anesthesia. One percent lidocaine (Xylocaine) with 1:100 000 epinephrine is injected into the area of the fossa triangularis on the lateral portion of the pinna, into the corresponding deep portion of the pinna to block cervical cutaneous innervation, and into the lower eyelid in the area where a subciliary incision is made. Topical anesthetic is applied to the patient's cornea, and a protective scleral shield is placed.

The auricular cartilage is harvested from the fossa triangularis of the ipsilateral ear (Fig 2, A). A U-shaped flap, anteriorly based, is elevated and the cartilage is harvested in such a way that perichondrium is left attached to both surfaces (Fig 2, B). The inferosuperior crura are left intact to avoid a cosmetic deformity. The cartilage is then trimmed and stippled with a No. 15 blade through perichondrium and cartilage on the lateral convex side, but not through the perichondrium on the deep side. This maneuver reduces the stiffness and curvature from the cartilage implant. The cartilage implant is trimmed and placed in such a way that it not only conforms to the general curvature of the globe but also to the infe-

Fig 1.—Paralytic ectropion: top, eyes open; bottom, eyes closed.



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rior border of the lower tarsus (Fig 2, B). The flap of skin on the pinna is sutured closed with a running 6-0 mild chromic suture, and the dead space is obliterated with 4-0 chromic mattress through-and-through sutures (Fig 2, C).

The cross-sectional anatomy of the eyelids is illustrated in Fig 3, A. The subciliary incision is placed about 3 mm below the lash line. First, the lower border of the lower tarsus is identified (Fig 3, B) and the inferior depressor muscles are separated from the tarsus so that a plane is developed immediately superficial to the conjunctiva. Then, the dissection is extended inferiorly to the level of the conjunctival cul-de-sac, about the level of the orbital rim (Fig 3, C). Next, the cartilage is inserted into this pocket and sutured with interrupted 8-0 nylon sutures to the lower border of the inferior tarsus (Fig 3, D and E). The skin is closed with a running interrupted 6-0 mild chromic suture. When a lower lid tighten-

Causes of Facial Paralysis Requiring Lower Eyelid Reanimation (October 1987 to March 1989)

Tumor	23
Acoustic neuroma surgery	16
Trauma (temporal bone fracture)	4
Congenital	4
Infection (otitis media or cholesteatoma)	2
Bell's palsy	1
Herpes zoster oticus	1
Total	**51**

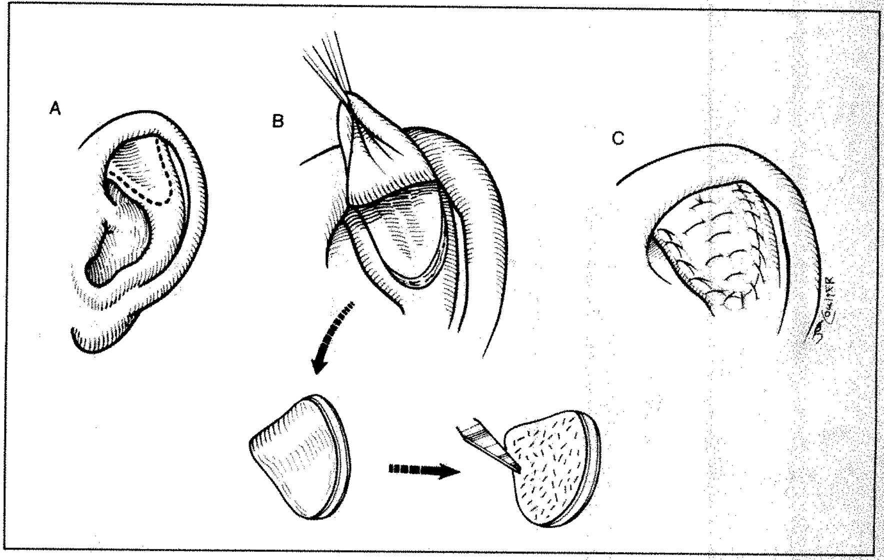

Fig 2.—Techniques: A, harvesting auricular cartilage; B, trimming and fitting cartilage; and C, suturing cartilage harvest site.

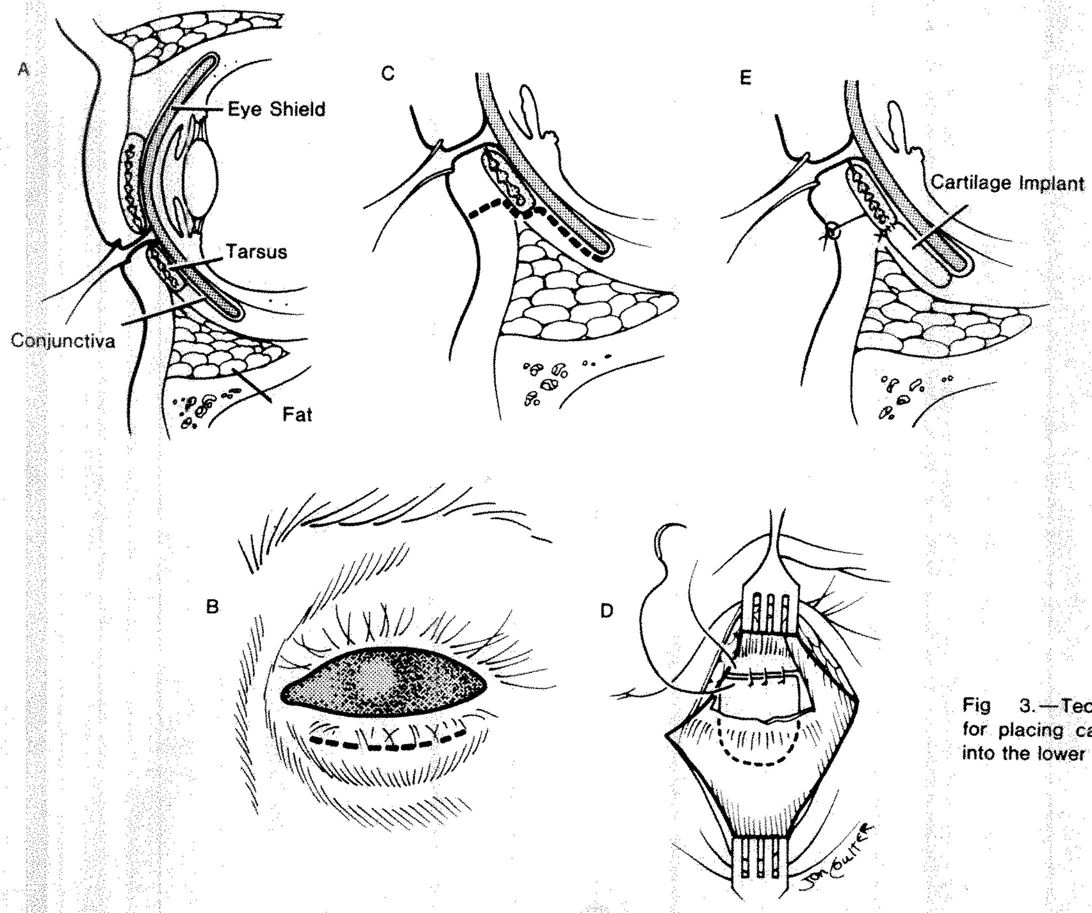

Fig 3.—Technique for placing cartilage into the lower eyelid.

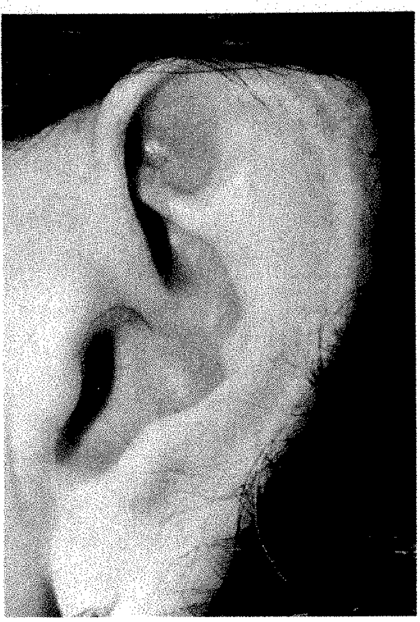

Fig 4.—Donor site, healed.

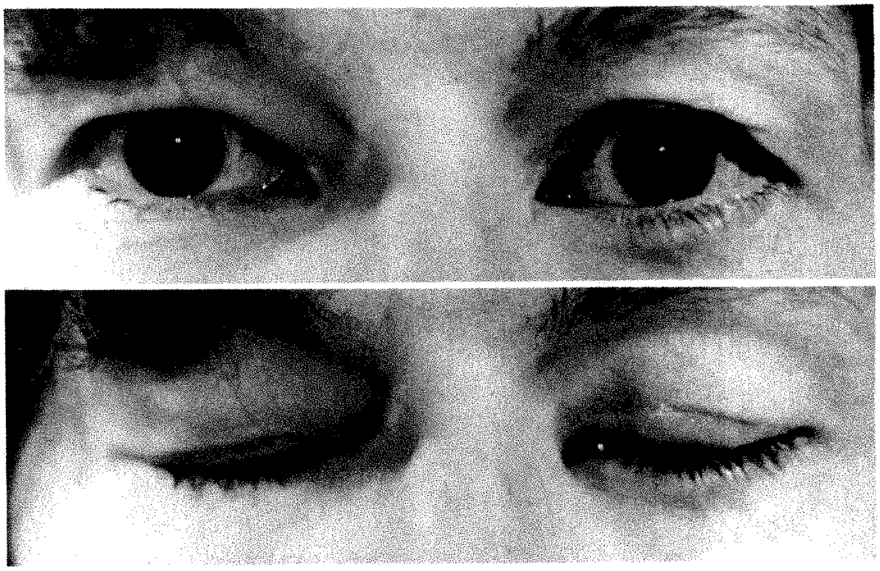

Fig 5.—After cartilage implantation: top, eyes open; bottom, eyes closed.

ing procedure (Bick procedure) is needed, it is performed after insertion of the cartilage implant to prevent tension on the lateral canthal repair, as the pocket for the cartilage implant is developed.

RESULTS

Fifty-one patients have undergone implantation of autogenous auricular cartilage to the lower lid over an 18-month period. Donor sites have healed well (Fig 4). All patients have had improvement in the position of the lower lid (Fig 5), and there have been no implant extrusions. In two of the initial 20 patients the cartilage migrated within a short time after surgery, necessitating revision surgery to resuture the cartilage to the lower border of the tarsus. In this first group of patients the cartilage had been sutured to the lower border of the tarsus using a 7-0 suture (Vicryl); after these two patients experienced slippage of the cartilage, the suture material was changed to 8-0 permanent ethilon, and no evidence of cartilage slippage has occurred in the last 25 patients operated on.

In the first 22 patients, the cartilage was external to the orbital septum and superficial to orbital fat, and in 3 of these 22 patients the cartilage was noticeable beneath the skin. Two of these 3 patients requested that the cartilage implant be removed, and in 1 patient the implant was placed in a deeper plane. These results led to revising the technique so that the cartilage is placed in a deeper pocket just over the conjunctiva. Since that time, 29 patients have been operated on with acceptable cosmetic results.

COMMENT

The use of autogenous auricular cartilage grafts to reanimate the lower eyelid has been described previously. Siegel[3] used conchal cartilage to correct involutional entropion by augmenting the tarsus, and found that the cartilage was stable for up to 5 years after placement. Matsuo et al[4] used conchal cartilage to line the lower eyelid posteriorly. Matsuo et al[4] had good results 6 months after surgery, and they noted that the results of using conchal cartilage were superior to those obtained using nasal septal cartilage. They attributed this to the fact that conchal cartilage is elastic and can be shaped to fit the shape of the globe.[4]

Robbins[5] described using a chondrodermal graft from the postauricular region for lower eyelid reconstruction. The cartilage was used to replace the missing tarsal plate.

Jackson et al[6] reported using conchal cartilage grafts for lower eyelid support in 41 patients, including 12 patients with paralytic ectropion due to facial palsy. The graft was placed under a skin-muscle flap and sutured above to the tarsal plate and below to the periosteum of the inferior orbital rim. They reported excellent results lasting up to 21 months after surgery.

The patients in our series have been followed for up to 18 months, and none has had evidence of resorption of the graft. These results, and those of other investigators, suggest that auricular cartilage remains stable in the eyelid and does not resorb.

Since this article was submitted, 40 additional patients have been treated with the cartilage implant for a total of 91 procedures. The technique has not been altered and the results continue to be excellent with one exception. The cartilage became infected in the 91st patient. On removing the cartilage, the infection cleared without any further problem.

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Management of Animal and Human Bites in the Head and Neck

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• Management of bites requires both local wound and systemic considerations. The authors will highlight their experience in 32 cases. Interestingly in this series, human bites were more common than animal bites. The bacteriology, antimicrobial therapy, and surgical treatment of human and animal bites will be reviewed. A management protocol that we use is based on whether the bite was inflicted by a human, dog, or other animal. The discussion will include cases demonstrating immediate and delayed reconstruction. Long-term follow-up was possible for a number of these patients.

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Animal bites to the face are more common than many realize, but management in many centers continues to be varied and contreversial. Using a reasonably standardized approach depending on the type and magnitude of the injury and the animal involved is possible and will yield consistently good results. Our series of 32 cases differs significantly from other reports in the literature.[1-4] At our institution, human bites are the most common animal bite of the face, most patients presenting within 4 hours of injury. Based on our experience, it appears that primary closure of human bite wounds is to be avoided. On analyzing our cases, a protocol for treatment has evolved that, when followed, should yield very acceptable results while avoiding the infectious complications associated with these types of injuries.

Unquestionably, our series is skewed. First, we are a surgical referral service specializing in head and neck problems. Second, our institution provides the only care available to a large, indigent population. This series reveals that while there is universal incentive to seek immediate medical care, the patient's concern for follow-up care does not mirror the early compulsion for treatment, once an acceptable outcome is likely. Long-term follow-up that may be more indicative of *our* concern for the ultimate functional and cosmetic result more accurately translates into the traditional noncompliant behavior often cited in this group of patients.

PATIENTS AND METHODS

Animal bites to the face are considered to be most often caused by a domestic pet, either a dog or a cat.[3-5] Our series consists of 32 patients with animal bites of the face and scalp treated by the otolaryngology–head and neck surgery department over a 7-year period. This series included 19 human bites, followed in decreasing incidence by dog (9), cat (2), rat (1), and hamster (1) bites. Sites of wounds are outlined in Fig 1 with the ear, cheek, nose, and upper lip being the more common areas involved. The total number of sites exceeded the total number of cases because several patients presented with multiple wounds.

The circumstances surrounding the human bites were easily separated into two fundamental scenarios, either an altercation or an amorous encounter. Although five human bites were the result of interactions between two retarded people, these were attributed to either anger or affection.

There were 15 males and 17 females in the series. The ages ranged from 9 days to 46 years, with the mean age being 26 years. Eight patients were younger than 10 years of age. Four patients were 10 to 20 years of age, twelve were 20 to 30 years of age, six were 30 to 40 years of age, and two were 40 to 50 years of age. The youngest patient was a 9-day-old infant who presented with an avulsed defect of the nasal tip resulting from a rat bite. The oldest patient was 46 years of age and presented with a partial avulsion of an auricle resulting from a human confrontation. There were 11 blacks and 21 whites in this series.

Clinical Presentations

Twenty-eight of 32 patients were initially evaluated by our department within 5 hours of injury. Wounds were identified as either early (within 5 hours of injury) or delayed (5 hours or later) presentation. Our series

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included 28 early presentations and 4 delayed presentations. The wounds were classified as punctures, lacerations, or avulsions. When there were a combination of injuries, the more serious was listed. Thus, a patient with a laceration or a puncture wound plus an avulsion was classified as an *avulsion*, and a patient with a puncture and a laceration was classified as a *laceration*. Using this classification, there were 3 punctures, 15 lacerations, and 14 wounds with loss of tissue or avulsions. Four patients with avulsion injuries (all of whom presented within 3 hours) presented with the missing tissue "in hand."

Management

Treatment is separated into four major divisions, in the absence of other injuries or extenuating circumstances: medical therapy, initial evaluation and wound care, primary surgical management, and wound care with delayed surgical management.

Medical therapy consists of appropriate tetanus vaccine, rabies prophylaxis, and antibiotic therapy. Rabies prevention must be considered in all nonhuman bites and initiated immediately, if indicated. This might include hyperimmune serum and active immunization. A tetanus toxoid booster should be administered if the patient has been immunized within the last 10 years. Tetanus immunoglobulin is necessary, if prior immunization has not been given.[1,4]

We routinely use intravenous ticarcillin and clavulanic acid (Timentin) for parenteral antibiotic treatment. If the decision is made to treat on an outpatient basis, antibiotic therapy with oral amoxicillin and clavulanic acid (Augmentin) is continued for a total of 10 days. Inpatients continued to receive intravenous ticarcillin and clavulanic acid in all cases until the time of discharge, when their therapy is switched to amoxicillin and clavulanic acid.

Initial wound care is extremely important and should be vigorous. Our routine is to use the jet lavage with copious amounts of isotonic saline. Débridement must be individualized, but the vasculature of the face makes routine surgical débridement an unlikely step in the management of most animal bites of the head and neck. However, obviously devitalized tissue should be carefully excised.

Puncture wounds are treated with pressure irrigation using a large syringe and an 18- to 20-gauge needle. Re-entry of puncture wounds with a needle allows maximum-pressure irrigation. It is important to take care to expose only the wound site to pressure to circumvent the untoward and extremely dangerous hydrodissection that is possible along tissue planes.

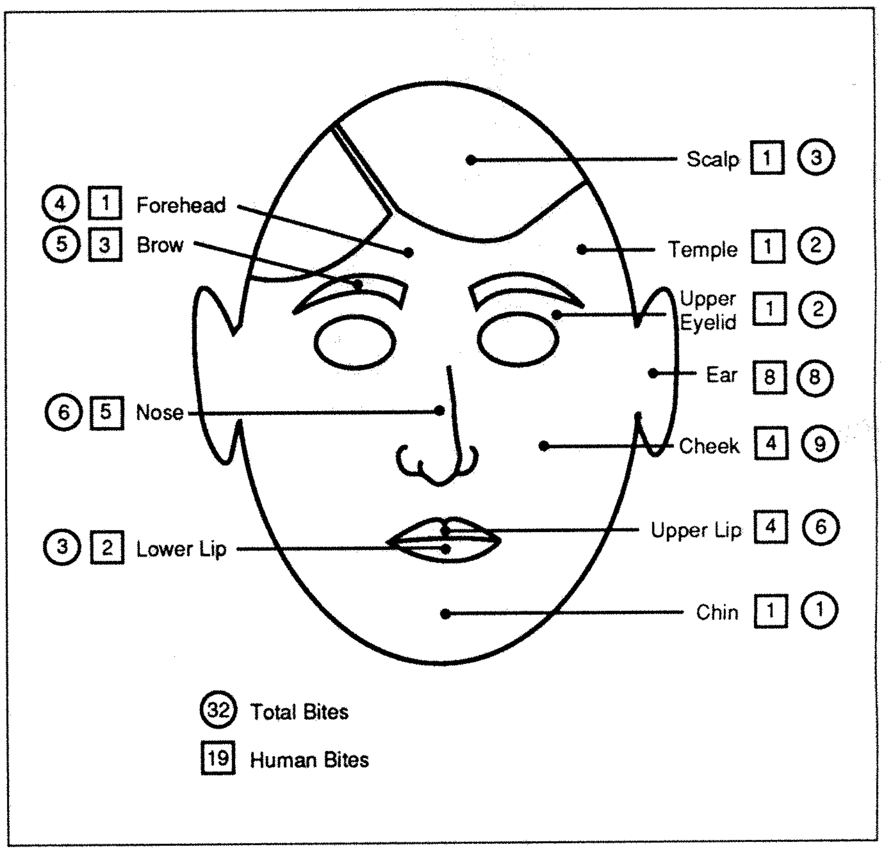


Fig 1.—Site of wounds. Total exceeds 32 because of injuries with more than one bite.

The decision on which treatment course to take depends on the source, site, character, and extent of the bite wound. Other important factors include the time interval from infliction of the wound to the institution of care, the age of the patient, and the likelihood of compliance. Surgical management is either primary repair or delayed reconstruction following appropriate wound care. Should the decision be primary closure or repair, the patient may be followed up on an outpatient basis. As with all bite wounds, antibiotic therapy should be continued for 10 days; patients admitted following initial surgical management and those selected for delayed repair continue to receive antibiotics intravenously. Interval wound care consists of continuous povidone-iodine soaks, changed frequently by the nursing staff or the able patient. The time required before optimum secondary closure is advised varies, but appears to be longer for human bites than for other animals. In our experience, the wound is ready for delayed repair in 2 to 5 days.

The review of our series revealed a striking observation. Four avulsion injuries were repaired quickly by surgically replacing the avulsed tissue as a free graft. All four patients were seen within 2 or 3 hours of injury; three of these patients presented with the avulsed tissue packaged in ice. (This is likely standard advice given by telephone from emergency-room personnel.) Three injuries in this group were human bites; one was a dog bite. Each injury was initially treated by scrubbing and jet lavage to decrease the innoculum prior to repair, and intravenous ticarcillin and clavulanic acid was begun immediately.

Figure 2 represents an avulsion injury of the auricle secondary to a human bite presenting within 1 hour of injury. The wound appeared clean and the avulsed tissue looked healthy and viable without maceration. The circumstances would appear quite reasonable for a primary repair using the patient's tissue as an autograft. A 3-year-old youngster sustained a clinically extremely clean, sharp, divitlike avulsion of the cheek by a dog (Fig 3). The missing tissue was clean and did not appear dissimilar from a graft harvested purposefully. The similarity of these patients is more profound in that both underwent a second surgical procedure, débridement of the dead graft on the fifth day postoperatively.

Our experience with four primary repairs of avulsion wounds using the patient's tissue as an autogenous graft has been a total failure. All infarcted tissue required more extensive débridement than just the avulsed part. Secondary management was possible but required extended delay (from 5 to 10 days). It is speculation, but these secondary repairs were likely not as ideal as would have occurred with an optimum secondary reconstruction. In all four cases, hospitalization and morbidity were increased.

Other avulsion injuries, most with more extensive or otherwise more compromised injuries, resulted in a superior reconstruction with far less morbidity and shorter inpatient confinements. A 9-day-old boy experienced an unfortunate confrontation with a rat (Fig 4). He sustained an avulsion injury to the tip of the nose and scratches on his cheek. The rodent chewed a divit of tissue that included a small portion of the lower lateral cartilages from the tip of the nose. The wound was managed in a delayed fashion until the avulsed injury clinically appeared clean enough for a secondary repair (48 hours after the injury). Reconstruction included a free perichondrial cutaneous graft from the patient's concha. The infant was discharged on the fifth day postoperatively. A 4-year follow-up indicates no stunting of nasal growth and an excellent cosmetic reconstruction.

A 24-year-old man was seen 2 hours following an amorous event that resulted in avulsion of a portion of his chin and lower lip tissue (Fig 5). Initial treatment included jet lavage, vigorous scrubbing of the wound and intravenous ticarcillin and clavulanic acid. The patient was admitted for wound management consisting of soaks with providone-iodine solution. The wound improved over the subsequent 4 days, allowing secondary surgical closure using a combination of advancement flaps on the fourth day after the injury. The patient was discharged on the second day postoperatively and has not returned for follow-up. We do possess information that his injury healed uneventfully.

Lacerations from dog bites in our experience do well with primary closure following jet lavage and antibiotic therapy, as described previously (Fig 6). Puncture wounds require no reconstructive decision but pose an infectious potential because of the difficulty in adequately cleansing the wound. We recommend high-pressure irrigation using a syringe with a needle re-entering the puncture wound sites. It helps to slowly rotate the needle so that it passes within the tract, rather than creating a new one.

A 3-month-old girl who was bitten by her brother on the auricle and cheek presented 4 hours following the injury with a 1-cm rock-hard edematous halo around the puncture teeth marks on the cheek and chondritis of the auricle (Fig 7). Intravenous ticarcillin and clavulanic acid was begun, fol-

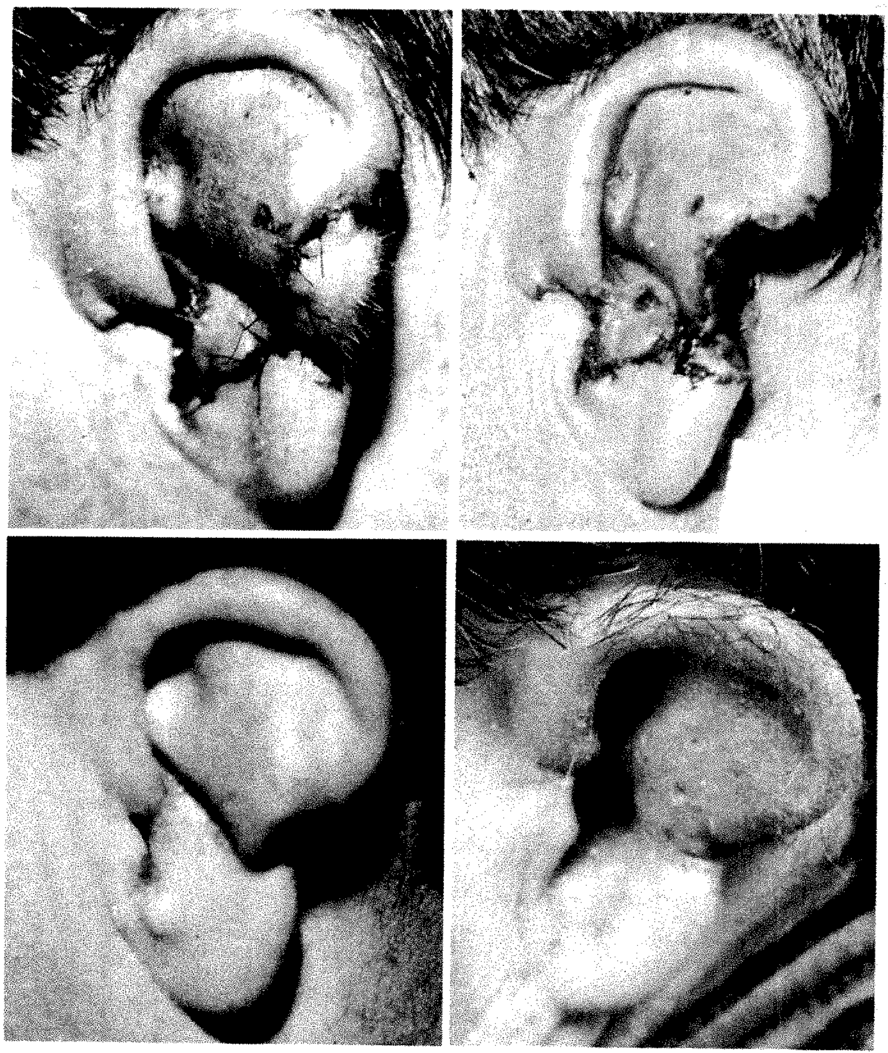
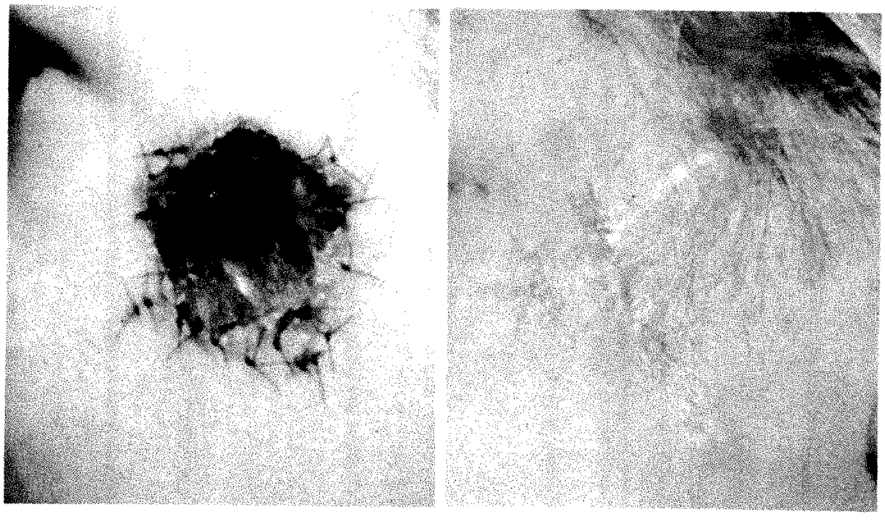


Fig 2.—Top left, Primary repair of avulsion injury of the auricle. Top right, Five days after the injury following débridement of dead graft. Bottom left, Three months after the injury with canal stenosis and chronic external otitis. Bottom right, Four months after meatoplasty using postauricular deepithelized flap technique.

Fig 3.—Left, Five-day postoperative primary repair of avulsed cheek wound. Right, Two years after the injury following two serial resections and scar revision.



lowed by high-pressure irrigation of the puncture wounds. The wound and the surrounding tissue quickly became markedly softer, and the induration had disappeared by 8 hours. She was discharged 48 hours following admission on a course of therapy with amoxicillin and clavulanic acid for 10 days and had an uneventful recovery.

COMMENT

Controversy exists as to the most appropriate management of animal bites. It is the view of some to treat most animal bites on an outpatient basis with primary surgical repair.[6,7] There are those who eschew primary surgical management.[8] The real problem exists with proper identification of what type of injury is involved. Our series consists only of patients referred to a head and neck surgical department, obviously eliminating many minor wounds and many more severe wounds located on other areas of the body.

Most authors are explicit in recommending thorough cleansing of wounds as essential in the initial management of bite wounds.[3,9] Subsequent therapy is quite controversial. There are those authors who are very conservative and those who believe most wounds can be managed safely with

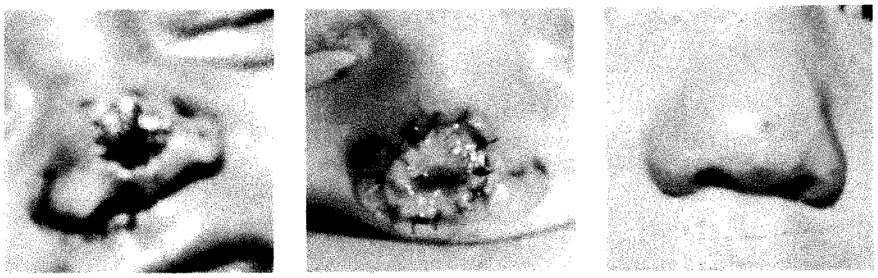


Fig 4.—Left, Acute rat bite injury. Center, Intraoperative secondary repair of nasal tip defect at 48 hours with perichondrial cutaneous graft. Right, Three-year postoperative view.

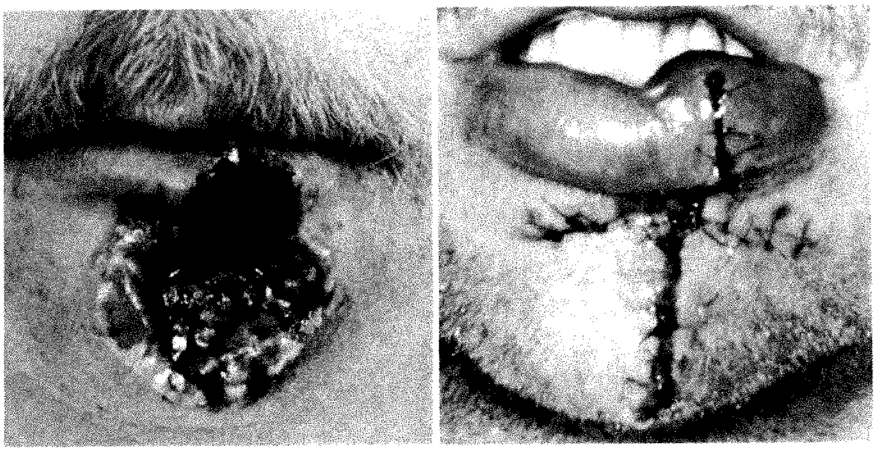
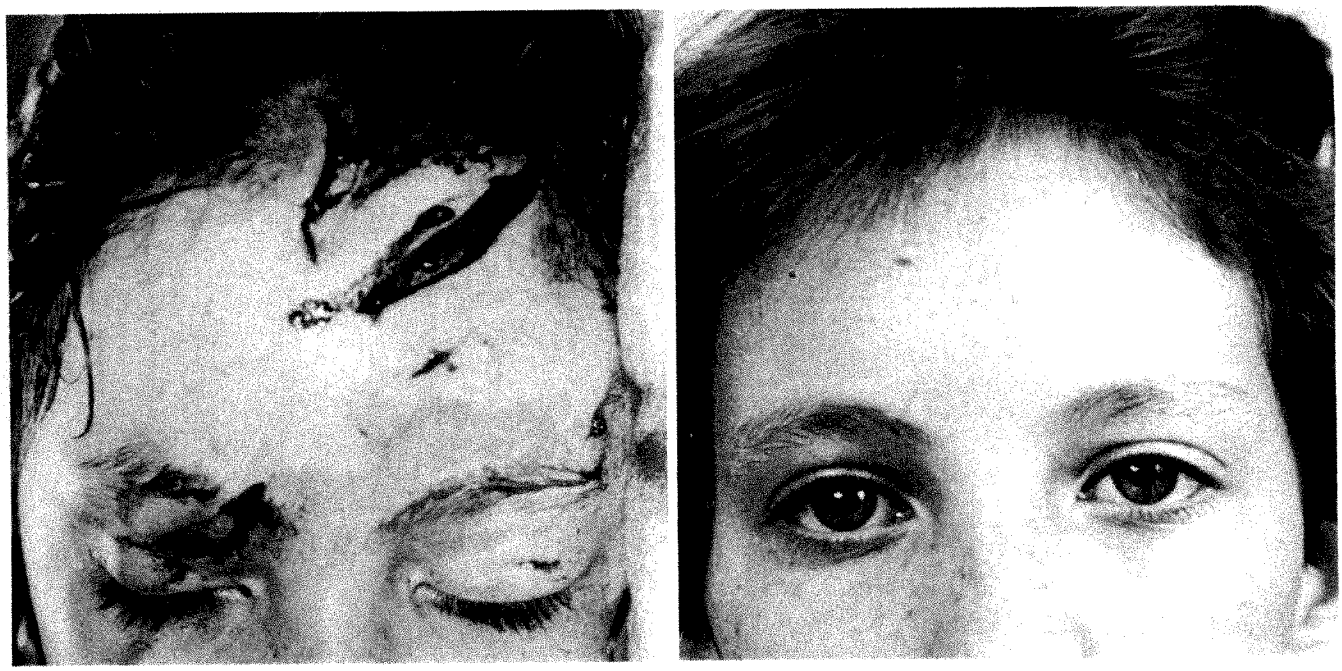


Fig 5.—Left, Human bite of lower lip and chin. Right, Secondary repair 5 days after the injury.

Fig 6.—Left, Multiple dog bite injuries. Right, Two months after the injury and primary repair.



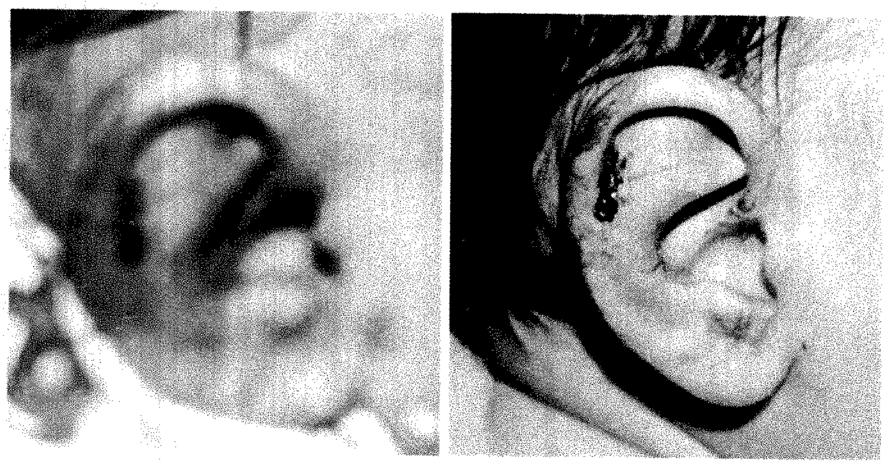


Fig 7.—Left, Four hours after a human bite of cheek and ear by patient's brother. Right, Twelve hours after initiation of intravenous ticarcillin and clavulanic acid (Timentin).

primary closure. It is clear that all authors are not speaking of identical injuries. The interval from the insult to the initiation of care, the circumstances surrounding the injury, the animal involved, the seriousness of the injury, and the location of the wound are just some of the obvious variables.

Another confusing aspect in the management of animal bites is the role of cultures and its significance in the choice of antibiotic therapy. We, presently, do not routinely obtain cultures unless the wound evidences necrosis or the patient does not show the expected improvement. Our pragmatic approach is based on analyzing our series and the discovery of much confusion and little clinical enlightment forthcoming when cultures were routinely employed.

Our choice of antibiotic therapy is also empirical, based on the literature[3,4,7,10] and our personal experiences. We employ ticarcillin and clavulanic acid in patients in whom intravenous administration is desirable. Those who are treated as outpatients and those who are treated with parenteral ticarcillin and clavulanic acid who are subsequently discharged are maintained on therapy with amoxicillin and clavulanic acid. The addition of clavulanic acid inhibits the action of the β-lactamase producers, and, thus, maintains the efficacy of antibacterial antibiotic therapy. These drug therapies also provide the broad coverage of antimicrobial activity necessary for the wide variety of bacteria present in bite wounds.

Delayed surgical management is indicated in all avulsion injuries and severe human lacerations. We have not always followed these precepts, which adds credence to our recommendations. Our present recommendations have been rigidly adhered to over the past 2 years. We have never experienced a satisfactory course from early autograft repair of avulsed tissue. On the contrary, we have had excellent results with our secondary reconstructions following delayed management of avulsion injuries. Currently, we treat all patients with animal and/or human bites to the face and scalp as outlined. We have arrived at these positions by some humbling experiences. It is our firm belief that cosmetic results are more predictable and the hospital stay shortened by prudent, delayed repair of avulsion injuries.

CONCLUSION

Animal bites introduce many variables to be considered; consequently, a management dilemma exists. There appear to be several reliable precepts to the care of this not-uncommon injury, based on our experience. By following a judicious therapeutic course, a more predictable and satisfactory outcome can be assured. We list five generalizations to be followed in managing animal bites of the head and neck.

1. The antibiotics of choice are ticarcillin and clavulanic acid for intravenous use and amoxicillin and clavulanic acid for oral use. We recommend a full 10-day course and do not routinely obtain cultures.
2. Immediate cleaning, scrubbing, and high-pressure lavage is important to decrease the inoculum.
3. Clean, nonhuman, laceration bites can safely be closed if seen within 5 hours of injury.
4. Severe human laceration bites are best treated in a delayed manner. Wound care consists of soaks with a povidone-iodine solution.
5. All avulsion injuries from any animal bite are managed in a delayed manner with secondary closure when the wound appears clinically clean.

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Dermal Healing After Local Skin Flaps and Chemical Peel

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• Like cells respond to injury through repair mechanisms unique for each cell type (eg, regeneration of the epidermis, granulation over exposed fat). How simultaneous chemical peel affects a local skin flap and why minimal differences in chemical peels can result in significant differences in outcome is not fully understood. In this study guinea pig skin was exposed to skin flap elevation, chemical peel, or a combination of the two. Biopsy specimens were taken at 3 to 35 days after injury and the histologic sections were studied. Results demonstrate that (1) lifting a flap causes changes in the subcutaneous tissue and reticular dermis that makes it more vulnerable to secondary injury and (2) the reticular dermis responds to injury as two physiologically distinct layers, although it appears histologically homogeneous. The upper reticular dermis heals by reorganization, while the deeper reticular dermis heals by scar formation. The differing response to injury of these cell layers may in part explain the low safety margin in aggressive chemical peels.

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Chemexfoliation (chemical peel) has been used by physicians in treating acne scarring, as an adjunct to facial plastic surgery for elimination of fine facial rhytids, and for reducing the risk of recurrent cutaneous carcinomas of the face for many years.[1,2] The main complications appear to be pigmentary changes, scarring, and cardiac arrhythmias.[2] The histologic changes induced by chemical peels have been described by several authors.[1,3-6] Stegman[3,4] demonstrated that the first 2 to 5 days of a peel result in epidermal necrosis with edema, homogenization, and lymphocytic infiltrates into the papillary and reticular dermis. At 2 weeks new collagen formation is evident in the dermis. Long-term histologic observations reveal a more organized dermis, smooth basement membrane, and a newly formed band of compact parallel collagen bundles in the dermis arranged horizontally to the surface, with numerous fine elastic fibers coursing through this layer. A sharp demarcation was observed between this and the underlying elastotic unpeeled dermis.[4]

When inflammatory changes are induced over a dermis that has been acutely altered, the mechanism of healing is dependent on the ability of the skin to reorganize the dermis and regenerate the epidermis. When used as an adjunct to cosmetic surgery, a chemical peel must penetrate the epidermis and cause a reorganization of the dermal collagen that is responsible for fine facial rhytids. Although the depth of injury is dependent on many factors, penetration to this dermal collagen layer is required for a cosmetically successful peel. As the inflammation subsides, the epidermis is regenerated from remnants in the hair follicles and rete pegs of the dermis. When the dermis is severely damaged, no epidermal regeneration occurs and wound healing is by second intention with scar contracture.

There has been recent debate in the literature over the effects of inflammation on acutely raised skin flaps. One school of thought proposes that inflammation may actually enhance survival through improving or protecting the vascular supply to a flap.[7-9] An extension of this theory is that the inflammation induced by a chemical peel would not damage an acutely raised skin flap (as in rhytidectomy). Another school of thought emphasizes that skin that has been surgically undermined should never be chemically peeled at the same time because full-thickness skin loss would inevitably result from further embarrassment of the vascular supply.[10,11]

We undertook a study on guinea pigs to determine if application of a standardized chemical peel to an acutely raised skin flap affects its viability. For this study, the flaps were designed as acutely raised cutaneous random pattern local flaps that were longer than would be expected to survive based on their size and blood supply. During this study punch biopsy specimens of peeled and unpeeled skin flaps, normal guinea pig skin, and skin exposed to a chemical peel without surgical manipulation were obtained for histologic comparison and the results are described in this article.

MATERIALS AND METHODS

Thirty-eight male Hartley white guinea pigs weighing 300 to 500 g were divided into three groups as follows: group A (n = 18), group B (n = 18), and group C (n = 2). For each of these animals, feedings were with-

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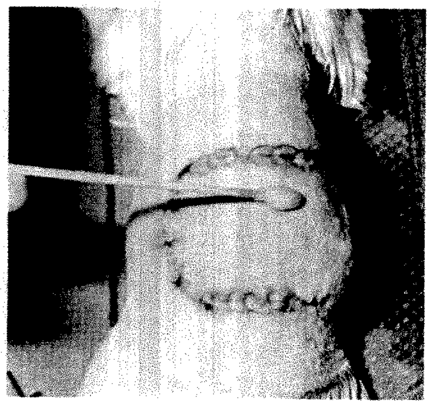

Fig 1.—Application of Baker's solution immediately after the skin flap has been sutured in place.

Table 1.—Summary of Histologic Findings

Time	Histologic Findings		
	Flap Only	Peel Only	Flap and Peel
3 d	Edema, vacuolization	Epidermal necrosis, dermal neutrophilic infiltrates	Epidermal necrosis, dermal necrosis, eschar formation
1 wk	Squamous hyperplasia, neutrophilic epidermal infiltrates	Focal adnexal necrosis, eschar formation, granulation	Total adnexal necrosis, granulation
3 to 5 wk	Deep granulation	Epidermal regeneration, collagen reorganization	Contracture, scar

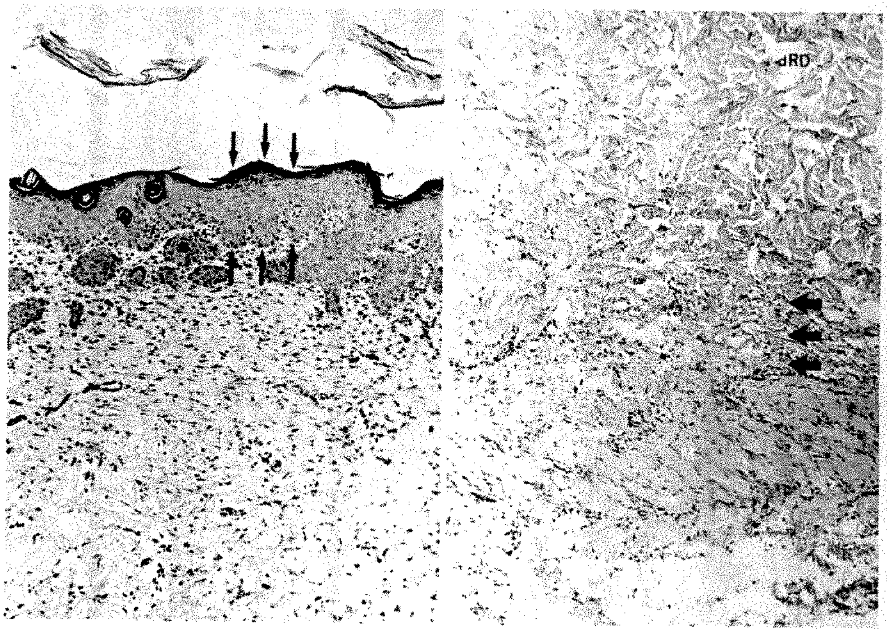

Fig 2.—Left, Skin flap without chemical peel at 2 weeks—epidermis. Squamous hyperplasia (arrows). Right, Skin flap without chemical peel at 2 weeks—deep reticular dermis (dRD). A diffuse inflammatory infiltrate is present in the subdermal muscle (M), with granulation tissue at the dermosubdermal tissue junction (arrows). The loose organization of the deep reticular dermis has been maintained.

held on the morning of surgery and hair on the back and sides was removed with electric clippers and a preparation razor from the nape of the neck to the tail. Anesthesia was induced with intramuscular injections of ketamine and xylazine, and the backs were prepared with betadine scrub, rinsed with sterile water, and then defatted with acetone. In groups A and B, 4 × 4-cm laterally based full-thickness skin flaps were then developed on the midline dorsum using sharp dissection. Visible blood vessels and the panniculus carnosus at the base of the flap were then divided sharply. Bleeding was controlled with light pressure, the flap and underlying tissues were irrigated with sterile saline and the flaps were replaced and secured in situ with interrupted 4-0 polyglactin (Vicryl) subcutaneous sutures and a running 4-0 polypropylene (Prolene) cutaneous suture.

In group A (controls, n = 18) the incisions were dressed with bacitracin ointment and no covering was placed on the flap. The sutures were removed on postoperative day 7 and flap necrosis was measured on postoperative day 21.

In group B (flap plus chemical peel, n = 18), Baker's solution was rolled onto the flap using a cotton-tipped applicator until the expected whitish discoloration appeared, indicating coagulation of epidermal proteins (one application layer in each case) (Fig 1). The Baker's solution was prepared as follows: 88% phenol 6 mL; tap water, 4 mL; hexachlorophene (soap), 1.3 mL; and croton oil, 0.5 mL. The solution was stirred frequently during application and a new batch was prepared each week of the experiment. Care was taken not to apply the peel solution directly on the skin edges that were then covered with bacitracin ointment. Tincture of benzoin was then painted around the flap 1 cm from the margins, paper tape was applied in two layers, and silk tape was applied over this. The tape dressings were removed 24 hours later, the wound was rinsed with tap water, and a light coat of bland emollient (eucerin) was applied to each flap with bacitracin applied over the suture line. The emollient and bacitracin were reapplied on postoperative days 3, 7, and 14. The sutures were removed on postoperative day 7 and flap necrosis was measured on postoperative day 21. In group C (chemical peel only, n = 2), the epidermis of the outlined flap was sharply incised without lifting the flap and Baker's solution was rolled onto the 4 × 4-cm area on the midline dorsum where flaps had been raised in the other subjects. This application was carried out in the same fashion as for group B, including postoperative care.

Two-millimeter punch biopsy specimens were obtained from the central portion of the surviving segment of all skin flaps and from the central portion of the two peel only flaps under light metofane inhalation anesthesia on postoperative days 3, 7, 14, 21, and 35. These are preserved in formaldehyde solution and subsequently sectioned for histologic study. When the final biopsy specimens were taken, a lethal dose of nembutal injected intraperitoneally was used for euthanasia.

RESULTS

Skin flaps demonstrated areas of obvious demarcation by 72 hours indicating areas of gross full-thickness skin loss. Gross comparison of peeled and unpeeled flaps at 21 days demonstrated a statistically significant increase in tissue loss in the flaps that

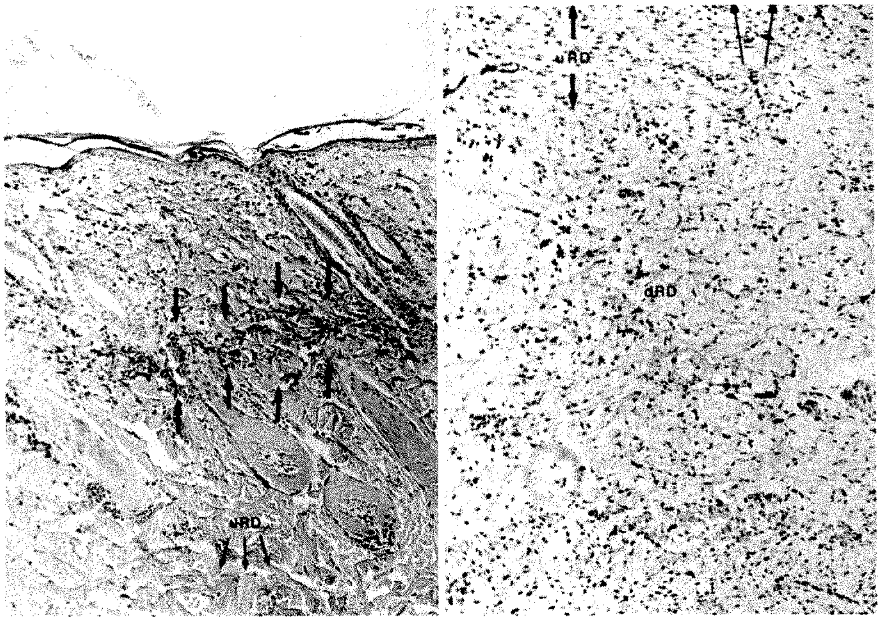

Fig 3.—Left, Chemical peel alone at 3 days—epidermis. A layer of inflammatory cells is present in the papillary dermis (arrows) with minimal penetration to the upper reticular dermis (uRD). Right, Chemical peel alone at 2 weeks—reticular dermis. A diffuse leukocytic infiltrate is present throughout the deep reticular dermis (dRD) without necrosis or alteration of the loosely organized stroma. The upper reticular dermis (uRD) shows evidence of early collagen realignment deep to epidermal appendages (E).

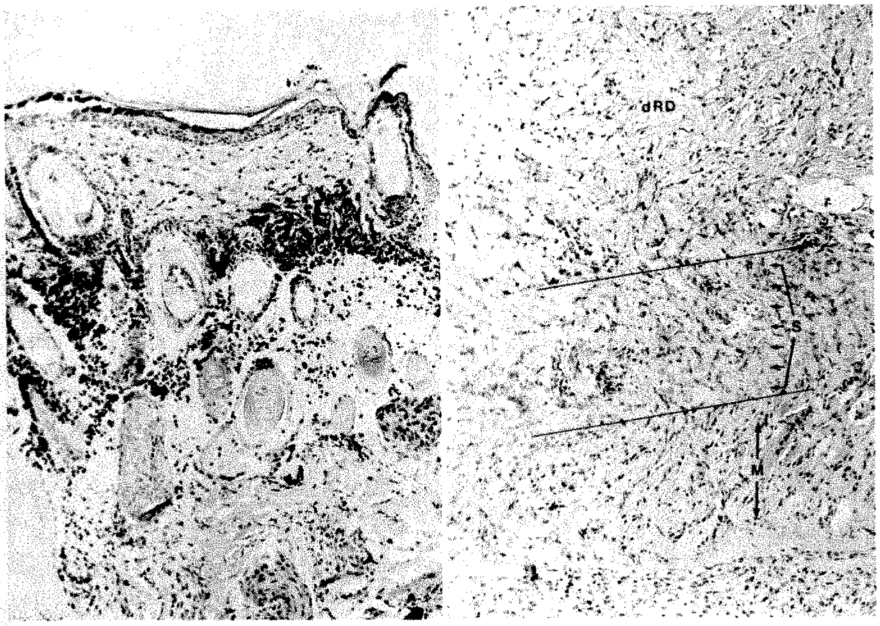

Fig 4.—Left, Flap and peel at 3 days—epidermis. Intense inflammation and necrosis of the papillary dermis is seen here (compare with Fig 3, left). This correlated grossly with the plane of separation of the eschar. Right, Flap and peel at 2 weeks—reticular dermis. The stroma of the deep reticular dermis (dRD) is more compact with some alignment of collagen. Granulation tissue has been replaced by scar (S) at the junction of the deep reticular dermis and subdermal muscle (M).

were simultaneously exposed to a chemical peel.[12] The histologic observations from each of the three groups are described below and summarized in Table 1.

In the unpeeled skin flaps, the epidermis, basement membrane, and support stroma in the surviving segments remained intact throughout the study. Ischemic change, including epidermal vacuolization and a 10% to 20% increase in epidermal cell layer thickness was observed in specimens at 3 days and at 1 week. Sparse lymphocytic and neutrophilic infiltrates were seen in the papillary dermis in the first week and these subsequently disappeared. Edema was obvious in the entire dermis from 3 days through 3 weeks. Neutrophilic infiltrates appeared in the deep reticular dermis and subcutaneous adipose tissues at 1 to 3 weeks and persisted. Grossly, this group demonstrated a mean flap necrosis of 3.11 cm². In those flaps that demonstrated full-thickness necrosis, granulation tissue appeared in the deep reticular dermis at 3 to 7 days and was most prominent at 3 weeks. There was no evidence of collagen reorganization (Fig 2).

Our observation of the histologic changes induced by peel alone paralleled those of Stegman and others.[3-6] Desquamation of the epidermis, loss of basement membrane definition, and edema with intense acute-phase neutrophilic infiltrates deep into the papillary dermis and upper portion of the reticular dermis were observed at 3 days. This was followed by epidermal sloughing with regeneration evident as early as 1 week and production of a smooth, more uniformly organized reticulin and collagenous layer in the papillary dermis from 3 to 5 weeks. Adnexal structures were focally destroyed by the neutrophilic infiltrate and were replaced by granulation tissue that became oriented parallel to the epidermal surface. Eschar separation was observed grossly at 7 to 10 days. Vascular spaces were more frequently engorged with blood (Fig 3).

In skin flaps exposed to simultaneous chemical peel, complete epidermal necrosis with eschar formation and sloughing was seen as early as 3

Table 2.—Mechanisms of Dermal Healing Compared With Skin Grafts*

Layer	Mechanisms of Healing	Type STSG
Epidermis	Regeneration	Thin STSG
Papillary dermis	Regeneration, realignment of collagen	Medium STSG
Upper reticular dermis	Regeneration, new collagen formation	Thick STSG
Lower reticular dermis	Granulation scar formation	Full-thickness skin graft
Subcuticular adipose and muscle	Granulation, scar, and contracture	Full-thickness skin graft

*STSG indicates split-thickness skin graft.

days, with subsequent healing similar to a full-thickness burn. Adnexal structures were totally destroyed by 1 week and did not regenerate. These flaps demonstrated intense neutrophilic infiltrates through the reticular dermis into subcutaneous adipose tissues, with scar formation occurring whether the deep reticular dermis appeared intact or was completely lost. Grossly, this group demonstrated a mean flap necrosis of 6.31 cm². Fifteen of the 18 flaps in this group demonstrated greater than 3 cm² of necrosis, with subsequent healing by scar formation and contracture (Fig 4).

COMMENT

Most of the nerve supply and all of the vascular supply of the skin is found in the dermis or subdermis. Capillary plexuses in the dermis not only supply the connective tissue but also are the only source of nutrients for the overlying epidermis and its derivatives that receive nourishment by diffusion from the dermis through the basement membrane. This blood supply is generally adequate to support the increased metabolic activity induced by superficial chemical burns. The fact that full-thickness dermal grafts can and do take indicates that the dermis and epidermis are capable of surviving through diffusion of nutrients alone.

The dermis is divided into a superficial papillary layer and a deeper reticular layer. The papillary dermis is characterized by a loose arrangement of relatively thin collagen fibers embedded in a layer of ground substance. The dermis papillae that are present between the epidermal rete ridges at the dermoepidermal junction, in combination with the dense pattern of thick fibers found in the reticular dermis layer are believed to be reponsible for fine facial rhytids. It is the reticular dermis that also contains the vascular, glandular, and neural elements of the skin, as well as the cells from which new collagen formation and complete epidermal regeneration may take place.

Dermal injury that is violent enough to cause destruction of collagen in the reticular dermis is also likely to damage the vascular supply found at that layer. Without this vascular supply, nutrients must diffuse from deeper layers to supply the epidermis. The deeper the injury, the greater the distance the nutrients must diffuse. Additionally, toxic by-products of increased cellular metabolism and cell necrosis must be removed through diffusion to the external surface or to deeper layers where the vasculature remains intact. Raising an acute skin flap further compromises the blood supply, increasing the diffusion distance.

The healing process observed histologically is readily compared with healing of donor sites from skin grafts (Table 2). The epidermis responds to injury by complete and identical regeneration of itself. The papillary dermis responds to injury by loss of adnexal structures and realignment or replacement of its collagen matrix. This process is believed to be in part responsible for elimination of fine rhytids by chemical peels. The reticular dermis appears to respond differently to injury depending on the depth of cells involved. This layer may in fact be composed of physiologically different layers.[13] The upper reticular dermis responds to injury in a similar fashion to the papillary dermis, ie, by realignment or replacement of its collagen matrix without contracture. The deep reticular dermis responds to injury by formation of scar tissue (Table 2).

The mechanism of healing of each layer of the skin is reviewed (Table 2). The application of a chemical peel over an acutely raised skin flap increases the tissue loss when compared with raising a flap alone. The final common determinant for skin loss after injury is the nutrient supply to those cells capable of regeneration of the dermis. Once these cells are damaged, the process of healing by scar formation appears irreversible. The deepest of these cell layers appears to be located in the deep reticular dermis. Further research on the location of this cell layer and the differences between it and the cells deep to it will enhance our understanding of the healing process.

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Wound Healing

Relationship of Wound Closing Tension to Scar Width in Rats

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• A study was conducted to better define the relationship between closing tension and the resulting scar width of incisional wounds. Five groups of 10 hairless rats each were studied. Transverse wounds were created and closed on the back of each rat, with closing tension varied by excising amounts of skin in widths of 0 (control), 15, 30, 45, and 60 mm. At 28 days, the scar width was measured by three methods: digital caliper, photographically, and histologically. Results showed that wounds closed under the highest tension (60-mm excision group) had significantly wider scars than controls by all three measurement techniques. Regression analysis of the caliper scar width as determined by squaring the closing tension resulted in a nonlinear equation resembling an exponential curve that "best fit" the variables.

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An inconspicuous, fine-line scar is an underlying goal of most facial plastic and reconstructive procedures. Using minimal tension at closure has been a cornerstone to obtain this final result. However, if too much tension is used, the end result is often a widened scar. But what is too much tension? When does closing tension become excessive and scar width begin to increase? Does scar width increase in a linear fashion with closing tension, or do large increases in closing tension need to occur before scar width is affected?

As part of a larger study that evaluated several characteristics of the healed wound in the hairless rat model,[1] the relationship of wound closing tension with the resulting scar width was investigated. By increasing and quantifying the closing tension of incisional wounds, the relationship of wound closing tension with the resulting scar width could be better defined.

Methods of measuring scar width were also investigated, as this technique of wound analysis has not been thoroughly described in the literature. This aspect of scar visibility should be objectively measured with reproducible techniques. This would allow for critical evaluation of visible results, and could be used as a method of comparing results among different surgical techniques of wound closure. Although wounds have been primarily judged by their strength with tensiometry studies, scar width is proposed as an equally important measurement of wound analysis. This is particularly true for surgeons who operate in the head and neck, where results remain visible.

HISTORICAL REVIEW

Biomechanical testing of the wound by tensiometry has been a standard method of wound analysis, in which scars are examined in vitro by pulling them apart with a uniformly increasing load. The stronger wound with the higher tensile strength has generally been considered superior. Scar width has been considered clinically important, but has only been quantitated in a few studies, and only in one study in which closing tension was considered as an important variable.

Winn et al[2] and Nilsson et al[3] compared different types of skin closure for uniform wounds in humans under no significant tension. Scars were measured in millimeters, but the measuring device was not clearly described. It appears to have been a basic ruler (0.5-mm accuracy).

Nordstrom and Nordstrom[4] compared the use of polyglycolic acid (Dexon) vs polypropylene (Prolene) as subcuticular sutures, comparing the scar width and depression between groups. Scalp excisions were performed in humans for alopecia, so wounds were placed under maximal tension at closure. Closing tension was not quanti-

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Table 1.—Group Means*

	Group 1	2	3	4	5
Skin excised, mm	0	15	30	45	60
Closing tension, g	10	18	39	84	165
Caliper scar width, mm	0.87 ± 0.33 (10)	0.97 ± 0.15 (10)	1.13 ± 0.36 (10)	1.27 ± 0.51 (10)	2.22 ± 1.47 (10)
Photographic scar width, mm	0.872 ± 0.804 (9)	0.538 ± 0.392 (9)	0.842 ± 0.672 (10)	0.823 ± 0.352 (7)	2.845 ± 1.828 (9)
Histologic scar width, mm	0.677 ± 0.283 (9)	1.209 ± 0.698 (9)	0.762 ± 0.213 (9)	1.988 ± 1.582 (9)	3.196 ± 2.708 (10)
Histologic scar area, mm²	0.655 ± 0.211 (9)	1.015 ± 0.565 (9)	0.626 ± 0.149 (9)	1.526 ± 1.533 (9)	2.851 ± 2.493 (10)
Histologic scar thickness, mm	1.208 ± 0.234 (9)	1.102 ± 0.270 (9)	1.121 ± 0.114 (9)	1.028 ± 0.101 (9)	1.086 ± 0.325 (10)

*Each group contained 10 animals. Values are means ± SDs. Numbers of animals measured are in parentheses.

tated, but the authors believed that they were all closed in a uniform fashion, as maximal skin was excised by the same surgeon. Wounds closed with polyglycolic acid were found to have significantly wider and more depressed scars than the polypropylene group. Scar width and depth were measured with a caliper (0.2-mm accuracy).

Several studies have shown that wounds with higher tensile strengths appear to have wider scars histologically. Scar clefts below the surface were wider, with more inflammation and more abundant collagen aligned parallel to the lines of tension.[5-11] These studies provided increased tension at the suture line in some fashion, but did not quantitate closing tension. In addition, the assessment of wider scar clefts by histologic examination was based on qualitative analysis without objective measurement data.

In the first report from this study,[1] we determined that wounds closed under tension developed higher tensile strengths at 28 days. The resulting tensile strength was related to closing tension in a logarithmic fashion, with the $\log_{10}$ of the closing tension resulting in linear increases in tensile strength. The 28-day period was chosen to demonstrate the effects of closing tension on tensile strength late in the healing period, and also to demonstrate the effects of closing tension on scar width, which is the subject of this article.

MATERIALS AND METHODS

The basic methodology of creating wounds with increasing tension in this study has been previously described[1] and is summarized below. Methods of measuring scar width are outlined in detail. The procedures in this project were conducted in accordance with the "Guide for Laboratory Animals and Animal Facilities and Care" as determined by the Laboratory Animal Resources Committee, National Academy of Science, National Research Council.

Table 2.—Hypothesis Test for the Means vs the Control (Group 1)

	Group 1	2	3	4	5
Caliper scar width, mm					
Scar width	0.87	0.97	1.13	1.27	2.22
Difference vs 1	. . .	0.10	0.26	0.40	1.35*
Photographic scar width, mm					
Scar width	0.872	0.538	0.842	0.823	2.845
Difference vs 1	. . .	0.334	0.030	0.049	1.973*
Histologic scar width, mm					
Scar width	0.677	1.209	0.762	1.988	3.196
Difference vs 1	. . .	0.532	0.085	1.311	2.519*
Histologic scar area, mm²					
Area	0.655	1.015	0.626	1.526	2.851
Difference vs 1	. . .	0.360	0.029	0.871	2.196*
Histologic scar thickness, mm					
Thickness	1.208	1.102	1.121	1.028	1.086
Difference vs 1	. . .	0.106	0.087	0.180	0.122

*Statistically significant ($P < .01$) by Dunnett's procedure.

Fifty hairless male rats of similar age and weighing approximately 250 to 300 g each received a pellet diet and water as desired, and were kept in polyurethane cages that allowed motion without running. Following the induction of anesthesia with ketamine (44 mg/kg) and xylazine (2.5 mg/kg intramuscularly), the back of each rat was prepared with a 10% povidone-iodine solution and washed with alcohol. Each rat then received a single 6-cm transverse skin incision midway between the sacrum and occiput and through the panniculus carnosus. This particular incision was chosen because it runs parallel to relaxed skin tension lines in rats and other small rodents.[6,11]

Five groups of 10 rats each were used. The first or control group received an incision without any skin excision. The four remaining groups received incisions that excised a rectangular specimen of skin in increments of 15 mm from the center of the wound. Different tensions were created by excising rectangles of skin 6 cm long and 15, 30, 45, or 60 mm wide to achieve increasing closing tensions. The goal was to increase tension in standardized increments up to a maximal closing tension for this animal model.

Animals were entered sequentially over a 6-month period into the various surgical groups in numbers of four to six at each surgical session. Animals would be entered into different surgical groups each time, rather than entering all the rats into each surgical group at one time. This allowed us to control for initial entry weight of the animals between groups, which has been shown to affect tensile strength[12] and thus also may affect scar width. Groups 1 through 5 were previously shown to be statistically similar with respect to entry and recovery weights.[1]

Calibrated strain gauges were used to measure the amount of force required to approximate each skin edge to the closing line. The closing line was determined by drawing the two wound edges together and marking the meeting point on the underly-

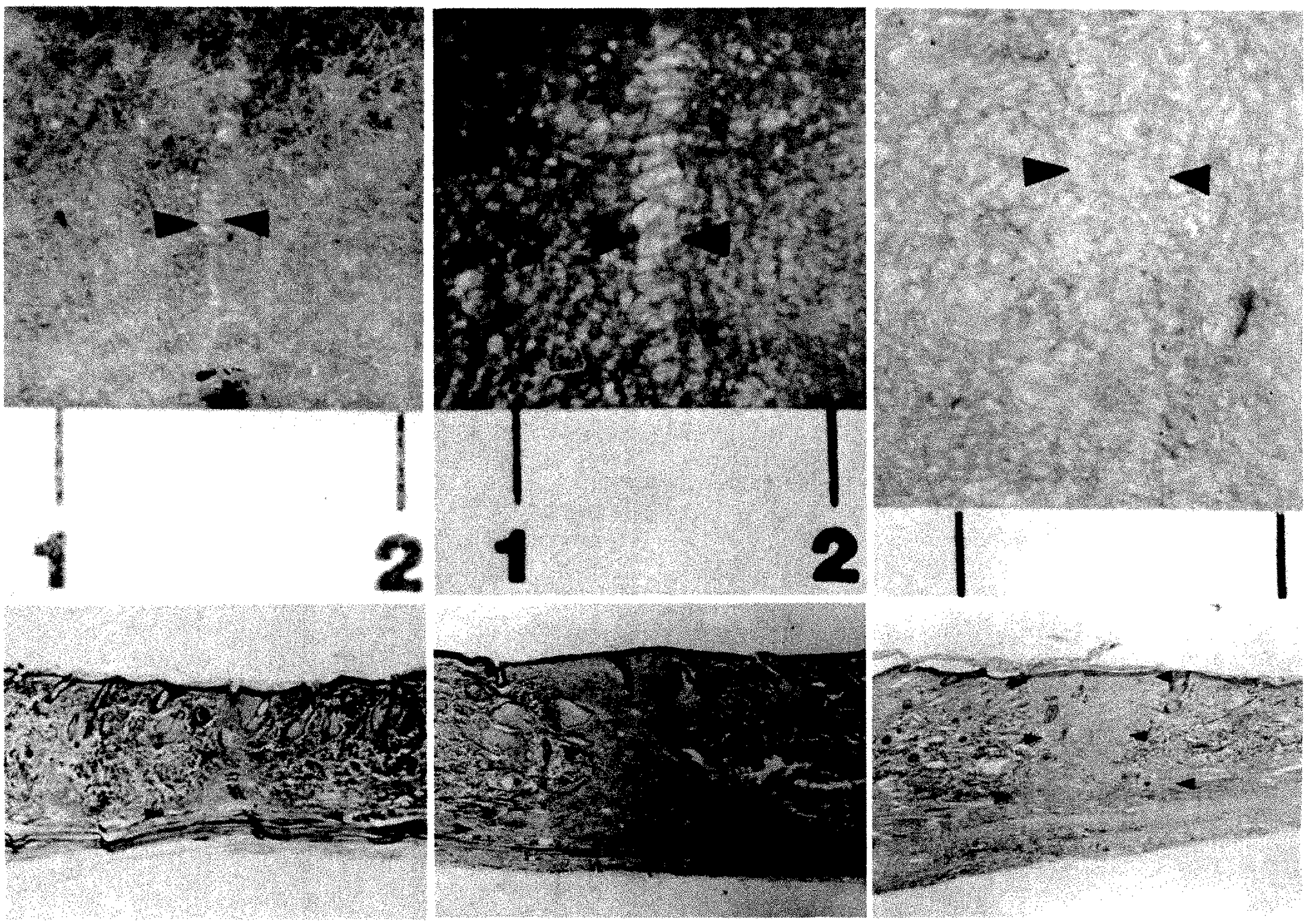

Fig 1.—Left (group 1), center (group 3), and right (group 5) represent minimal, intermediate, and maximal tension groups, respectively. Each photographed scar is shown above its corresponding histologic section (hematoxylin-eosin, ×250). The arrows outline the scar/scar cleft. For histologic measurements, the distance between the upper two arrows would represent the scar cleft width (in millimeters), and the area encircled by the six arrows would represent the scar cleft area (in square millimeters).

ing fascia. Three measurements were then taken for each wound edge, with the mean considered to be the closing tension. The total closing tension of the wound was considered to be the sum of the means of each side.

The wound edges were not undermined in order to control for vascularity. All wounds were closed with a running 5-0 nylon suture and cared for in a standard fashion. At 7 days the sutures were removed, and at 28 days the rats were killed in a halothane chamber. Measurement techniques A and B (described below) were conducted in vivo, and the specimen was excised in a 6 × 8-mm rectangle and pinned to a corkboard to the in vivo dimensions. Portions of the scar were then submitted for tensiometry and histologic examination. Histologic specimens were pinned to paraffin sheets to the in vivo length, immersed in Bouin's solution for 2 hours, and placed in formaldehyde solution. The use of Bouin's solution helps prevent shrinkage of the specimen during processing.[11]

Scar Analysis

Scars were measured by the following three methods. Suture tract scars were not included in any of the measurements.

A. The wound was measured in vivo by a digital caliper (0.01-mm accuracy) at the widest point in the central portion of the wound. Five measurements were taken at the same point, the highest and lowest values were excluded, and the mean was calculated from the remaining three values. The operator (G.V.M.) was blinded as to the group the animal was in, and was not able to see the digital readout until after the measurement was completed. Loupes (×3.0 magnification) were worn while measuring to assist with scar identification.

B. The wound was marked with the specimen number with a label including a millimeter scale. Photographs were taken of the in vivo wound at a fixed focal distance, including the scale within the photograph, with the scar marked at the 1.5-mm point on the scale to assist later with its identification. These 35-mm slides were later enlarged to ×75 by projection onto a computer-assisted digitizing pad, and the scar width and millimeter scale were measured (0.001-mm accuracy) in a blinded fashion by one of us (L.P.A.B.). The actual scar width was then calculated and recorded from one measurement. This measurement was not necessarily taken from the same location as the caliper measurement. If the edges of the scar could not be clearly identified on the photograph, the photograph was excluded.

C. Three cross-sectional hematoxylin-eosin-stained slides were obtained for each wound. Slides were numbered differently than the rat number by an independent observer prior to measurement. Therefore, measurements were blinded, with the code being broken after all the measurements

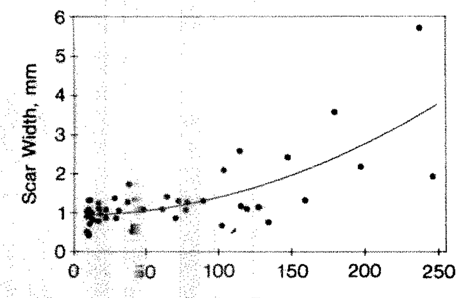

Fig 2.—Closing tension vs caliper scar width. The curve is represented by the equation $y = 0.942 - 0.000045635x^2$, where y represents scar width (in millimeters) and x represents closing tension (in grams); $r = .724$ and $P < .0001$.

were taken. Using a microscope-based computer-assisted digitizing pad, three measurements were obtained by one of us (G.V.M.): scar cleft width immediately below the surface, scar area from epidermis to muscle layer, and scar thickness (0.001-mm accuracy). Scar collagen was readily distinguished from unwounded collagen on histologic examination. One set of measurements was made on each slide, with three slides per scar. The mean of these three readings was submitted for statistical analysis. If the scar was not clearly identified or not cut in true cross section, the slide or group of slides from this rat was excluded.

Statistical Methods

Dunnett's procedure[13] was used to compare the different tension groups (2 through 5) with the control group (1). Critical D values were determined for two-sided comparisons between the four treatment groups and the control group for $P < .05$ or $P < .01$.

An unweighted least-squares regression analysis was performed to determine the "best fit" curve relating closing tension to tensile strength. Residual analysis was conducted to determine the random error.

RESULTS

The mean values of the scar width analysis are shown in Table 1. Although there were 10 rats in each surgical group, the measurement groups for the photographic and histologic measurements have less than 10, since data were excluded as explained above. Six cases were excluded from photographic analysis because it was difficult to determine where the edge of the scar was on the projected slide.

Statistical analysis with Dunnett's procedure is shown in Table 2. Wider scars were demonstrated by all three methods of scar width analysis for the maximal tension group (5) compared with the control group. Differences were highly significant at $P < .01$. There was no statistical difference in scar thickness between groups by histologic measurements.

Figure 1 shows characteristic photographs of the visible scar on top, and photomicrographs of the corresponding histologic appearance below for groups 1, 3, and 5. Histologic scar width would be the distance between the upper two arrows, while histologic scar area would be the area surrounded by all six arrows.

Using an unweighted least-squares multiple regression of the caliper scar width as determined by squaring the closing tension, a nonlinear equation "best fit" the variables as demonstrated in the scatterplot (Fig 2), with $r = .724$, residual mean square = 0.3564, and $P < .0001$. The equation for the curve is $y = 0.942 + 0.000045635x^2$, with y representing scar width (in millimeters) and x representing closing tension (in grams). Standard assumptions for the regression model were checked using residual analysis. The random error was normally distributed (Wilk-Shapiro = 0.9001).

COMMENT

This study was primarily conducted to help determine the relationship of closing tension with scar width. To accomplish this, we also investigated and defined different techniques of scar width analysis, since only three previous studies have used scar width as the end-point to be measured. Studies by Winn et al[2] and Nilsson et al[3] probably measured scar width using a ruler (0.5-mm sensitivity), and Nordstrom and Nordstrom[4] used a mechanical caliper (0.2-mm sensitivity). With recent advances in digital technology, sensitivity was greatly increased for the methods used in this study over previous reports. We realize that some of our measurement techniques are evolving and will require refinement in the future. However, we view this study as a continuing step toward objectively quantifying one of the visible characteristics of a scar.

Scar width was measured by three methods in this study: in vivo with a caliper, with a computer digitizer of the in vivo photograph, and with a computer digitizer of the histologic slides. The caliper method was probably most representative of the visible scar on the skin's surface and most reliable. Measurements were obtained in a blinded fashion under magnification with a digital caliper (0.01-mm sensitivity) with reproducible results. This technique would be useful in any in vivo situation in which recovery of the scar was not possible or not planned. It would be particularly applicable to longitudinal studies of scar width analysis, where scars are evaluated on several occasions over long periods.

The photographic method was investigated because of its obvious advantage of providing a permanent visual record of the scar. Placing the enlarged image on a digitizing pad also improved sensitivity (0.001 mm) and reproducibility. The main disadvantage was that it was often difficult to determine where the edge of the scar was on the two-dimensional photograph. Scars are three-dimensional and are made visible by subtle lighting changes between the normal surrounding skin and the scar's edge. These lighting changes may not be discernible following flash photography and when transferred to a two-dimensional plane.

We are now marking the edges of scars with India ink prior to taking the photograph. The scar on the photograph can then be measured later on the digitizer between the two ink marks. This eliminates the need for three-dimensional visualization of the scar at the time of the photographic measurement.

Histologic measurement of the scars was conducted as an adjunct to the other measurement techniques, and to investigate its usefulness since it has not been previously described. Scar cleft width immediately below the epidermis was measured, as well as dermal scar width area between the epidermis and the superficial muscle layer (panniculus carnosus). We felt that this would be another way of objectively quantifying results, and that one might expect the scar cleft width and area to be characteristic of the overlying scar. Fine line scars would be expected to have small scar cleft widths and areas, while those with wider scars on the surface would be expected to have larger histologic values. The histologic data appear to generally correlate with the caliper data, showing increases in width and area as closing tension increased, but not in the same progressive curve demonstrated for the caliper width (Fig 2).

Although the means followed similar trends between measurement techniques, there was not always correlation in measurements between techniques for each individual scar. One problem was identifying the scar on the photograph, and a second was that measurements for all techniques were not taken at exactly the same location within a given scar. This is important because scar width can vary along the length of a scar. In ongoing research, we are attempting to make the photographic and caliper measurements at the same location, and are tattooing this location with ink to mark the site for longitudinal measurements or histologic measurements at recovery. However, despite these controls, even a slight variation of 1 to 2 mm along the scar's length where the width is measured can cause differences in values.

Scar width was noted to be statistically higher in group 5 (highest tension) than group 1 (controls). This was noted with all three methods of scar width analysis, and lends support for any of these methods in subsequent studies with the above-mentioned changes. Caliper and photographic techniques lend themselves to clinical or longitudinal studies, while histologic evaluation adds another technical analysis to correlate the other data if the scar is recovered.

Dunnett's procedure[13] was used to compare groups 2 through 5 with the control group 1. This test is similar to Student's *t* test in its application, but it is a stricter test against chance occurrence. This is necessary since four experimental groups were statistically compared with the control group. This would make finding a difference by chance occurrence more likely, and Dunnett's procedure takes this into account.

The SDs of means (Table 1) showed wider variations in scar width in the higher-tension groups. Like the *t* test, the SDs are taken into consideration by Dunnett's procedure when calculating *P* values. Despite higher SDs in group 5, the differences in means between group 1 and 5 were still highly significant for all three measurement techniques ($P < .01$).

The scatterplot (Fig 2) was derived from caliper measurements of the scar, since it was believed to best represent the visible scar width. It indicates that scar width will initially increase slowly in a linear fashion in relation to closing tension, then increase in a gently sloping exponential fashion at higher tensions. Below 75 to 100 g of tension, there is little change in scar width. Above this point, scar width rises more rapidly. It should be remembered that this model is only applicable for closing tensions less than 250 g. One might expect that scar width will reach a plateau once a certain closing tension is reached.

Higher tensions could not be studied due to the small size of this animal model. Due to the similarities to human skin, porcine dermis might be useful to study these higher closing tensions, and also to test the proposed model for closing tensions less than 250 g. We suspect there would be only minor differences in healing, as tension is probably universally detrimental to forming narrow scars. Because tension may be redistributed differently depending on the animal model or the anatomic location, the curve may be shifted to the right or left based on these variables, and the exact values may vary. Likewise, the *y* intercept or narrowest scar without any closing tension may shift up or down.

The proposed model supports what happens in clinical practice. Wounds closed under "minimal" or "normal" tension almost uniformly heal with a fine line scar. However, once a "critical" degree of tension is reached, scar width and scar formation become more unpredictable. At times these scars will be acceptable, and at other times they will be wide and require revision. This is probably the exponential portion of the curve where smaller changes in closing tension can cause wider swings in scar width results.

Our previous report[1] showed that tensile strength increased as closing tension increased at 28 days, and therefore wounds closed under tension were stronger and considered "superior." This report showed that scar width also increased with closing tension, and wounds closed under tension were wider and considered "inferior." Both factors must be taken into account when evaluating a wound, as well as the surgical arena one is working in. A stronger wound might be superior in tendon or abdominal wall repair, but a narrow scar cleft is equally desirable in neurorrhaphy or on the skin of the face. We propose that scar width/cleft analysis is as important as tensile strength analysis in studying the healed wound when appropriate, and must be considered as surgeons investigate methods of creating the "ideal" scar.

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Effect of Local Hypothermia on Early Wound Repair

Ramon M. Esclamado, MD; Gregg A. Damiano; Charles W. Cummings, MD

• Local hypothermia has been shown to enhance survival of pedicled skin flaps. The effect of prolonged local hypothermia on an important clinical correlate, wound healing, is examined in this study. Skin incisions were made on each flank of nine female pigs, and these incisions were closed primarily. A cooling pad was applied over the incisions on the right side of each animal, achieving an average dermal temperature of 35°C vs 39°C for the control side. Four animals were treated for 72 hours postoperatively; five pigs were treated for 7 days. Wound repair was evaluated by standard histologic techniques at 24 hours, 72 hours, 7 days, and 14 days. Control wounds in all animals demonstrated the normal progression of primary wound repair. We demonstrate that local hypothermia: (1) inhibits wound repair for the duration of its application; (2) is not detrimental to the early 2-week phase of wound healing if applied for 72 hours postoperatively; and (3) may have a beneficial effect by inhibiting inflammation through delay of the late inflammatory phase of wound healing.

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Locally applied hypothermia has been shown by Kiehn and Desprez[1] and Desprez and Kiehn[2] to enhance the viability of pedicled flaps in a rabbit model by delaying the onset and reducing the severity of necrosis. They proposed that local hypothermia altered skin circulation, reduced lymphatic flow, and, most importantly, reduced cellular metabolism.

In a recent study in our laboratory (George S. Goding, MD, unpublished data, 1988), local hypothermia was shown to reduce cutaneous flood flow in the panniculus carnosus porcine myocutaneous flap model to levels where flap necrosis would be expected using the dermatofluorescence index as the predictive test.[3] However, there was no difference in flap necrosis between treatment and control groups. A delayed onset of flap necrosis was demonstrated in the hypothermic group.

The possibility arises that accompanying the reduction in cutaneous blood flow is a concomitant decrease in edema and inflammation. Through the reduction in inflammation, local hypothermia could have an additional application in the early mobilization of donor sites for osseocutaneous revascularized grafts used for mandibular and craniofacial reconstruction, ie, the shoulder for the scapular osseocutaneous free flap. However, the effect of prolonged *local* hypothermia on an important clinical correlate, wound healing, has not been examined. This study evaluates the effect of prolonged local hypothermia on early (2 weeks) primary wound repair.

MATERIALS AND METHODS

Surgical Procedure

Nine 10- to 15-kg female pigs were used in this study because the blood supply and histologic characteristics closely resemble human skin.[4] All animals were treated in the following manner: general anesthesia was induced intramuscularly with ketamine (35 mg/kg) and xylazine (5 mg/kg), then maintained with halothane after endotracheal intubation. Both flanks were shaved and prepared with povidone-iodine solution, then draped. Using aseptic technique, a series of four 2-cm-long vertical skin incisions were made on each flank. Each incision was made sharply through the skin, dermis, and subcutaneous fat until muscle tissue was identified. Bleeding was controlled with local pressure, any blood clots were gently wiped from the wound, then all wounds were closed primarily with three simple interrupted sutures of 4.0 monofilament nylon (Fig 1).

To minimize the effect of wound tension on healing, skin incisions were made vertically in the relaxed skin tension lines and standardized in their location. Wound 1 was made 5 cm from the vertebral column and 4 cm caudad to the posterior border of the scapula. Wound 3 was made 10 cm caudad to wound 1, maintaining the same relation-

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Reprints not available.

ship to the vertebral column. Wounds 2 and 4 were made in a row, 4 cm more ventral on the flank and also 10 cm apart. As shown in Fig 1, this results in wound 2 being located 5 cm caudad and 4 cm ventral to wound 1, and wound 4 maintains this same relationship to wound 3.

Local Hypothermia

A cooling pad that covered all four wounds was applied to the left flank of each pig (Fig 2). A nonfunctioning cooling pad was not applied to the control flank to duplicate conditions normally used in the clinical setting, ie, wounds covered with dressing vs wounds covered with a cooling pad and dressing.

To minimize pressure effects from the dressing that would affect both control and treated flanks, the cooling pad was secured to the left flank with adhesive tape (noncircumferential) and then a circumferential dressing was applied that covered both flanks. The dressing consisted of a 4-in gauze wrap covered by 4-in expandable tape. In addition, the dressing was changed after wounds were harvested on days 1 and 3. The dressing was then removed after day 7. Therefore, the growth of the pig during this period did not result in a constrictive dressing that would affect wound healing.

The pig was then awakened and attached to a thermotemperature machine (HOT/ICE, Hollister Inc, Libertyville, Ill) via a 1.8-m-long two-way circulating hose. The thermotemperature machine can maintain an alcohol/water mixture over a temperature range of 4.40°C to 40.5°C and circulates this cooled alcohol/water mixture through the cooling pad to provide controlled, local hypothermia to the surface in contact with the pad. Local hypothermia (10°C) was applied to the left side of five pigs for 7 days postoperatively. Four pigs were subsequently treated for 72 hours postoperatively; however, due to technical problems with kinking of the circulating hose, three of these animals were treated with hypothermia from 60 to 72 hours.

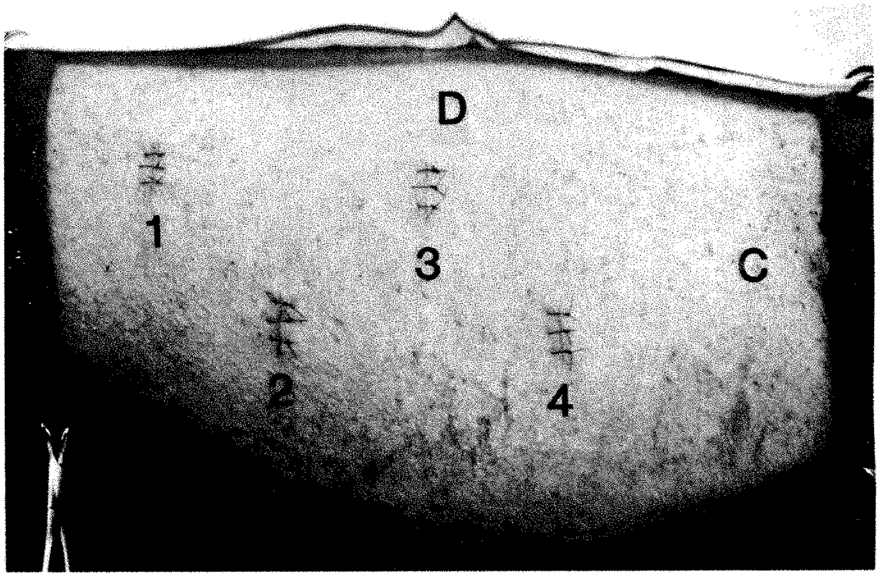


Fig 1.—This is a representative photograph that illustrates the size and location of skin incisions on the left flank of a pig (see "Materials and Methods" section). Skin incisions were made on both flanks. C indicates caudad; D, dorsal. Wounds are labeled 1 through 4 and harvested in numerical order with the corresponding wound on the opposite flank.

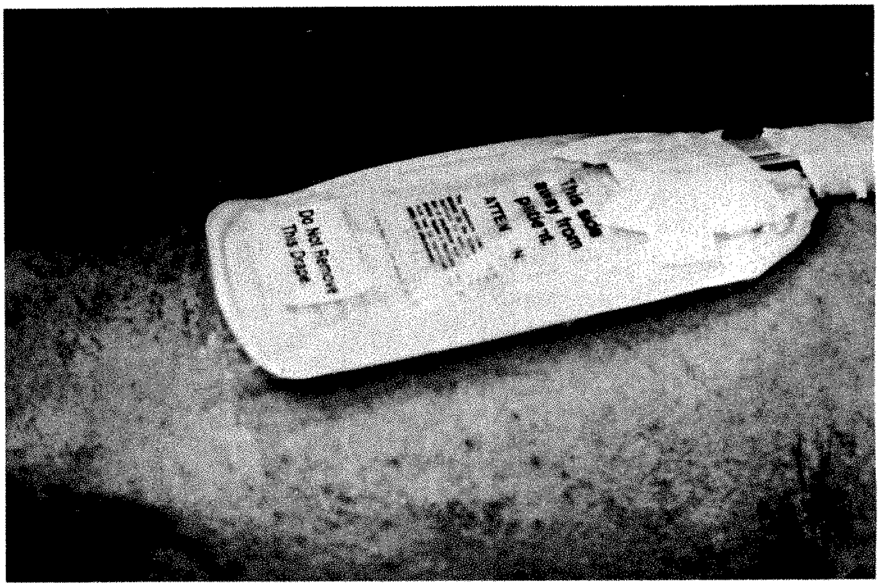


Fig 2.—This photograph shows the cooling pad through which the alcohol/water mixture is circulated. Note that the cooling pad covers all wounds on one flank simultaneously.

Wound Harvesting

On postoperative days 1, 3, 7, and 14, wounds 1, 2, 3, and 4, respectively, were harvested from both the treated and contralateral control side. In four animals, after the induction of anesthesia, the thermotemperature machine was turned off and the dermal temperature was immediately measured with a sharp intracutaneous thermal probe (YSI, Tele-thermometer, Yellow Springs [Ohio] Instrument Co Inc), first on the cooled skin and then on the contralateral control skin. Measurement of dermal temperatures was performed on days 1 and 3 on three animals and on days 1, 3, and 7 in one animal, for a total of nine temperature comparisons.

Each wound was then harvested in an elliptical fashion to include the subcutaneous fat layer and approximately 0.5 to 0.75 cm of normal skin on each side of the wound. The resultant defect was undermined for approximately 2 cm and closed primarily. The cooling pad was reapplied to the left side in all animals on postoperative day 1, and on postoperative day 3 for those five animals receiving local hypothermia for 7 days. The total time that the cooling pad was off during wound harvesting was 60 to 90 minutes. All wounds were fixed in 3.7% formaldehyde solution in phosphate-buffered saline (at a pH of 7.4) for 24 to 48 hours. A 0.3- to 0.5-cm-thick section of each wound was dehydrated through a series of ethanol and methyl salicylate and then embedded in paraffin using standard histologic techniques. Sections, 10 μm thick, were cut perpendicular to the long axis of each wound and mounted for histologic examination.

Wound Healing

Each wound was examined by 12 sections at 100- to 200-μm intervals. Six sections were stained with hematoxylin-eosin and the cellular infiltrate was examined. The time of appearance of acute inflammatory cells (polymorphonuclear leukocytes [PMNs]), chronic inflammatory cells, and fibroblasts were compared with treated and control wounds for each animal at each time point. The remaining six sections were stained with Gomori's one-step trichrome stain for collagen and the time course for epithelial healing and the appearance of collagen in the treated and untreated wounds were compared.

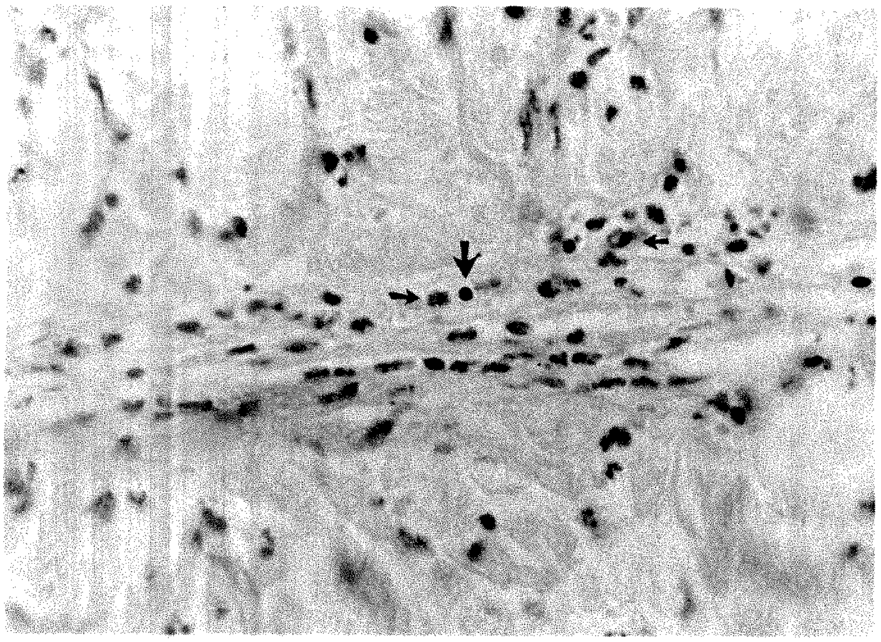


Fig 3.—High-power photomicrograph of fibrin clot of day 1 control wound. Note abundant inflammatory cell infiltrate consisting primarily of polymorphonuclear leukocytes (small arrows) with occasional mononuclear cells (large arrow) (hematoxylin-eosin).

RESULTS

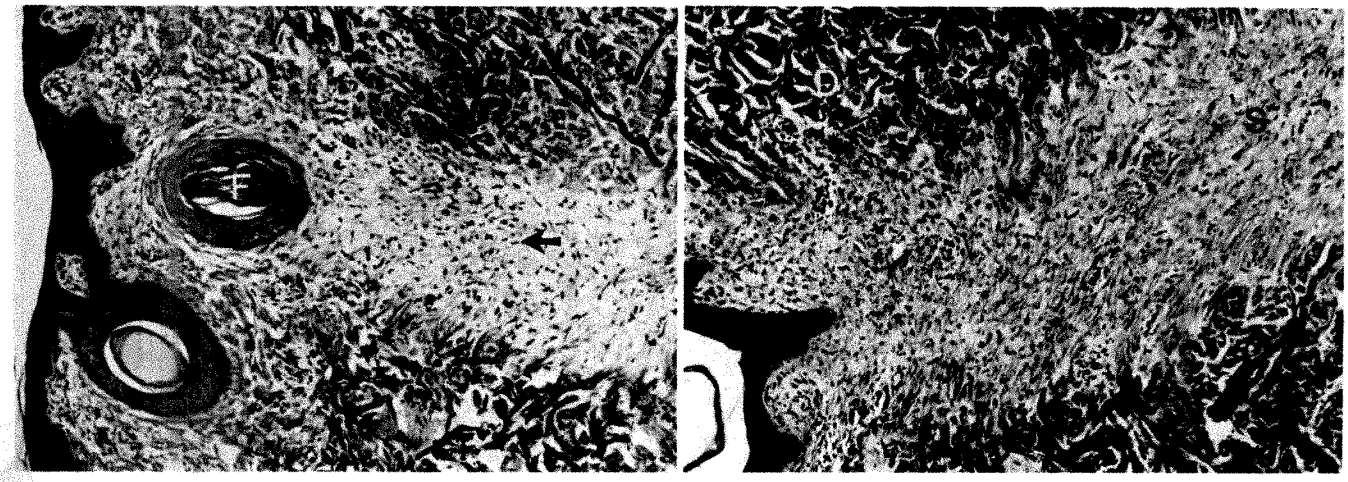
Skin Temperature

The dermal temperature on the control skin on all nine determinations was 39.0°C. The mean dermal temperature for the cooled flank skin was 34.5°C, with a range from 34.0°C to 35.0°C. Since this difference in skin temperature (approximately 4.5°C) was constant among four animals, we assumed that this temperature gradient was the same in the remaining five animals, since the temperature regulator on the thermotemperature machine was set at 10°C for all animals.

Early Wound Repair

Control Wounds.—Control wounds in all nine animals showed the normal progression of primary wound repair. Intact epithelium bridged the wound surface by 24 hours. Early-phase inflammatory cells (PMNs) were present by day 1 as the predominant cell type, although monocytes were also present (Fig 3) and had migrated into the fibrin clot. Late-phase inflammatory cells (monocytes) and fibroblasts were predominant by day 3. Collagen depo-

Fig 4.—Healing in control wounds assessed by trichrome-stained sections for collagen. Left, Control wound harvested at 7 days showing early cellular scar (arrow), which is easily distinguished from surrounding darkly stained normal dermis. Several hair follicles (F) are seen, as well as healed epithelium on the left. The wound contains numerous stellate nuclei likely representing fibroblasts and a fine random meshwork of collagen fibrils that have not formed well-defined fibers that are seen in normal dermis. Right, Control wound harvested at 14 days demonstrating densely staining collagen in scar that now forms well-defined fibers that are beginning to align perpendicular to the long axis of the wound. S indicates scar; D, dermis.



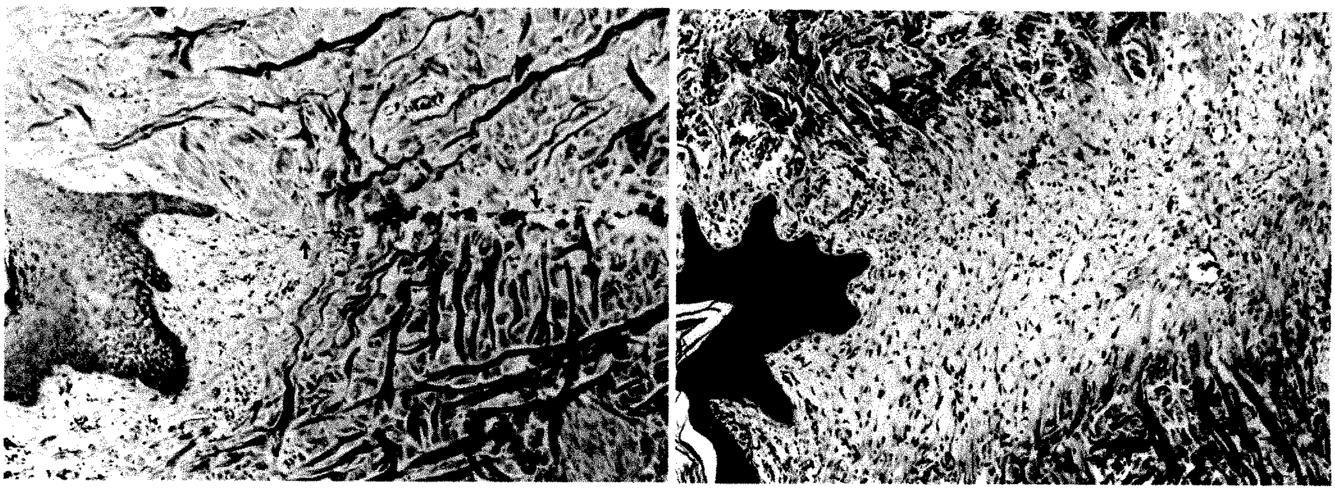


Fig 5.—Healing in wounds treated with 7 days of local hypothermia. Left, Wound harvested at 7 days demonstrating a relatively hypocellular wound and absence of newly synthesized collagen (arrows). Right, Wound harvested at 14 days demonstrating random meshwork of collagen fibrils with blood vessels. This wound appears similar to that shown in Fig 4, left.

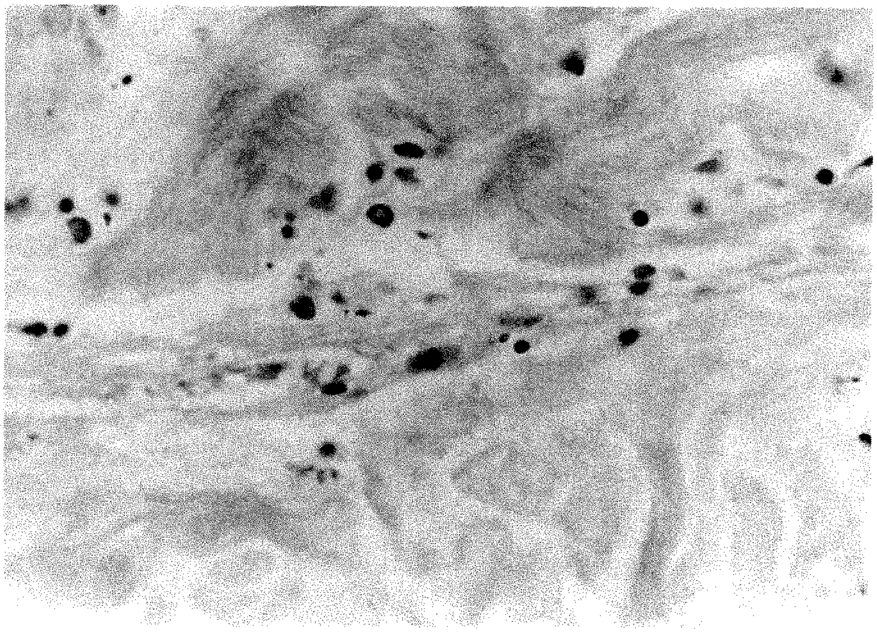


Fig 6.—High-power photomicrograph of a wound harvested at 7 days that was treated with local hypothermia for 7 days. Note relative hypocellularity with few monocytes and fibroblasts (hematoxylin-eosin).

sition was present by day 7 (Fig 4, left) and was abundant by day 14 (Fig 4, right).

Seven-Day Hypothermia.—Wounds treated with prolonged hypothermia (7 days) demonstrated a relative absence of early wound repair for the duration of time that the wounds were cooled. Epithelial repair was delayed until day 7 in three of five animals and was not observed until day 14 in one animal. Collagen deposition was not present at 7 days (Fig 5, left). Although PMNs were present within 24 hours, there was a relative lack of late-phase inflammatory cells and fibroblasts on day 7 (Fig 6). However, by day 14 collagen was present (Fig 5, right) and the wound appeared similar to the 7-day control wound (Fig 4, left). These findings were consistent in four of five animals treated for 7 days. The fifth animal, because of logistic reasons, did not have the 7-day wound harvested until day 8, although the cooling pad was removed on day 7. This wound showed the presence of healed epithelium and collagen deposition on day 8 (data not shown). Although this is an isolated finding in one animal, it suggests that healing is not completely arrested during the duration of hypothermia and is possibly rapidly initiated when cooling is discontinued.

Three-Day Hypothermia.—Four animals were then treated with 3 days of local hypothermia to determine if the previously observed delay in wound repair was strictly a function of the duration of application of cold. We observed in the treated wounds of all of the pigs that the epithelium had healed by day 3 and collagen was present on day 7 (Fig 7, left). By day 14, the wound appeared similar to a 14-day control wound (Figs 7, right, and 5, right, respectively). Polymorphonuclear leukocytes were present by day 1 and the appearance of late-phase inflammatory cells and fibroblasts was delayed until day 7. Figure 8 is a schematic representation of the aforementioned histologic findings for the three treatment conditions.

COMMENT

One of the most important aspects of wound healing is the rate at which a wound gains tensile strength. Ordman and Gillman[5] have shown in skin inci-

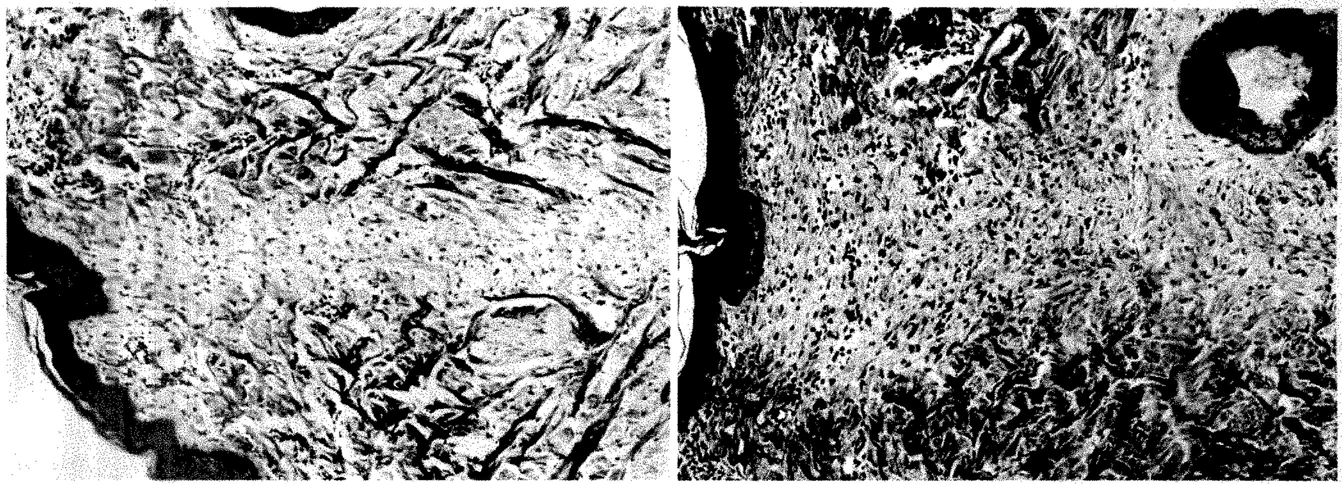


Fig 7.—Healing in wounds treated with 3 days of local hypothermia. Left, Wound harvested at 7 days demonstrating the presence of collagen fibrils and healed epithelium. Right, Wound harvested at 14 days demonstrating an abundance of collagen, but less well oriented than Fig 5, right.

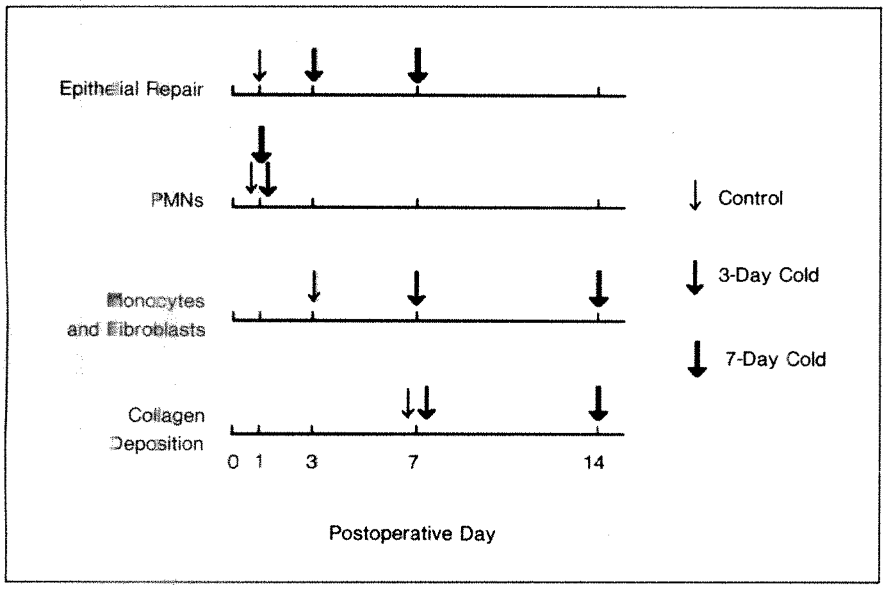


Fig 8.—Comparison of early wound repair for treatment groups and controls. Epithelial repair, onset of late inflammatory phase, and collagen deposition are all delayed for approximately the duration that local hypothermia was applied. The early inflammatory phase (polymorphonuclear leukocytes [PMNs]) was not affected.

sions in pigs that only approximately 10% of the tensile strength of a mature wound is present at 2 weeks. Tensile strength was subsequently not used in this study as a parameter for wound healing, since a small, but significant, effect of local hypothermia would be difficult to demonstrate unless a large number of animals are used and/or the technique for measuring tensile strength is highly accurate, with a small standard error.[6]

The basic biological mechanism in cutaneous tissue repair has recently been reviewed by Clark.[7] The first 2 weeks are characterized by an inflammatory stage, granulation tissue formation, and early matrix formation and remodeling (collagen accumulation). The early inflammatory stage consists of an early phase where PMNs predominate (although monocytes are present), whose function is to rid the site of injury of contaminating bacteria. The later phase is highlighted by the predominance of monocytes and their conversion to macrophages, which seems to be critical for the initiation of tissue repair. Granulation tissue formation is heralded by the presence of macrophages, fibroblasts, and neovascularization in a matrix of collagen, fibronectin, and hyaluronic acid. This peaks at approximately day 7. Collagen accumulation and early remodeling then occur.

With this background in mind, we chose to qualitatively assay early wound healing by determining the onset of epithelial repair and collagen deposition. Suppression of inflammation was examined by determining the time course of the appearance of PMNs as a marker for the early phase and monocytes/macrophages for the late phase.

Our results for the control wounds confirm the observations made by Ordman and Gillman,[4] regarding the normal progression of wound healing in pigs. Locally cooling wounds to 4°C to 5°C less than the control appeared to inhibit wound healing for the duration that the cold was applied. Both epithelial repair and collagen deposition were delayed (Fig 8). It is interesting to note that the group treated with 72 hours of hypothermia demonstrated healed epithelium at 3 days and the presence of monocytes and fibroblasts by day 7. In contrast, the group treated for 7 days with hypothermia did not develop healed epithelium until day 7 and the late inflammatory phase was not evident at day 7. This discrepancy can possibly be explained by the fact that the 3-day treatment group actually received local hypothermia for 60 of the first 72 hours. This serves to illustrate that epithelial repair is a rapid process and that the inhibitory effect of local hypothermia is a rapidly reversible effect. This observation was also applicable to collagen synthesis, since the 3-day treatment group demonstrated the presence of collagen in the 7-day wound, although in qualitatively less quantity than the control. The ultimate effect of prolonged hypothermia on tensile strength, however, is not known.

It was our initial hypothesis that prolonged local hypothermia may be useful by inhibiting the inflammatory response, thereby allowing early mobilization of a donor site. Our results generally indicate that the acute early inflammatory phase is not inhibited, since PMNs were present in abundance in day 1 wounds of both control and treated wounds. The late phase of inflammation, composed of monocytes and macrophages, appeared to be inhibited by local cold. Since macrophages release a variety of biologically active substances, including vasoactive mediators and chemotactic factors that facilitate the recruitment of additional inflammatory cells,[7] inflammation may be suppressed, although the ideal method for determining the extent the inflammation is suppressed would be direct quantitative measurement of these vasoactive mediators.

We conclude as follows: (1) local hypothermia inhibits wound repair as measured by epithelial repair and onset of collagen deposition for the duration of its application; (2) inhibition of wound healing is rapidly reversible after removal of local cooling; (3) local hypothermia is not detrimental to the early 2-week phase of wound healing if applied for 72 hours postoperatively; and (4) local hypothermia may have a beneficial effect by inhibiting inflammation through delay of the late inflammatory phase of wound healing.

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Original Articles

Anesthetic Complications of Tympanotomy Tube Placement in Children

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• The anesthetic risks during placement of tympanotomy tubes were prospectively studied in 510 children. Complications were analyzed according to patient risk factors, anesthesia regimen, and surgical variables. No complications were seen in 423 (82.9%) children. Minor degrees of upper airway obstruction (treated with jaw thrust, oral airway, or positive pressure ventilation) were encountered in 61 patients (12.0%), 1 patient had minor obstruction and bradycardia, and 7 patients (1.4%) experienced more severe airway obstruction. Vomiting occurred intraoperatively in 2 patients (0.4%) and postoperatively in 9 patients (1.8%). Twelve patients (2.4%) experienced other complications, including cardiac dysrhythmias, transient hyperthermia, fall from the transport stretcher, and transient agitation. Four patients experienced multiple complications. Patient age, history of anesthesia, and level of experience of the anesthetist were all related to the type and frequency of complications. Anesthesia given for placement of ventilation tubes into tympanic membranes is relatively safe; however, these data are applicable to patients treated by pediatric anesthesiologists in the setting of a children's hospital.

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The placement of tympanotomy tubes with the patient placed under general anesthesia is the most commonly performed minor surgical procedure in children in the United States today. Its brevity, where induction and awakening of the patient are the time-limiting factors, may lead physicians to minimize the potential risks of this procedure when obtaining informed consent from parents. To our knowledge, no prospective study has been performed to elucidate the specific and actual risks of anesthesia during this procedure.

PATIENTS AND METHODS

Five hundred ten children undergoing bilateral insertion of tympanotomy tubes at the Children's Hospital of Buffalo (NY) were studied prospectively from July 1987 through March 1989.

A complication was defined as any physiologic variation from normal, including vomiting, cardiac dysrhythmias, and airway obstruction. Complications were identified and recorded by the attending pediatric otolaryngologist with agreement from the pediatric anesthesiologist. At the first postoperative visit, parents were questioned regarding complications occurring after discharge, particularly vomiting.

Anesthetic Technique

All patients received preoperative atropine, either orally or intramuscularly. Induction was accomplished with mask anesthesia using fluothane, oxygen, and regular or high nitrous oxide concentrations that were given to 491 patients. The remaining 19 patients received other combinations of anesthetic agents in the operating room at the discretion of the anesthesiologist. The anesthesia was administered by one of the following: student nurse anesthetist, nurse anesthetist, resident, fellow, or attending anesthesiologist. The person holding the mask was designated as the "anesthetist." All procedures were directly supervised by an attending pediatric anesthesiologist.

Data Collection

Patient variables that were analyzed included age, previous general anesthesia, the presence of craniofacial abnormalities, the presence of chronic medical abnormalities such as cardiac disease, respiratory disease, neurologic disorders, endocrine disorders, and the presence of an upper respiratory tract infection (URI) on the day of surgery. A URI was defined by the presence of one or more of the following symptoms: cough, rhinorrhea, congestion, sore throat, or fever. Beginning in October 1988, patient sta-

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Table 1.—American Society of Anesthesiologists (ASA) Physical Status Classification

ASA 1, normal healthy patient
ASA 2, patient with a mild systemic disease
ASA 3, patient with a severe disease that limits activity, but is not incapaciting
ASA 4, patient with an incapacitating systemic disease that is a constant threat to life
ASA 5, moribund patient not expected to survive 24 hours with or without operation

Table 3.— Mean Age in Relation to Complication

	n	Age, y	SD	*P*
No complications	419	3.8	3.0	>.05
Any complications	83	3.9	3.5	
Airway complications	64	3.1	2.8	<.01
Nonairway complications	19	6.9	4.0	
Vomiting complications	11	8.0	2.0	<.01
Nonvomiting complications	72	3.3	3.1	

Table 2.—Summary of Anesthetic Complications Associated With Tympanostomy Tube Placement*

Complication	No. (%)
None	423 (82.9)
Airway obstruction	68 (13.3)
Mild	61 (12.0)
Severe†	7 (1.4)
Other complications	
Vomiting	11 (2.2)
Intraoperative	2 (0.4)
Postoperative mild, no treatment	7 (1.4)
Postoperative severe, treatment	2 (0.4)
Dysrhythmia	9 (1.8)
Bradycardia	6 (1.2)
Premature ventricular complexes	3 (0.6)
Temperature elevation, transient	1 (0.2)
Agitation	1 (0.2)
Fall from stretcher in recovery room	1 (0.2)

*The number of complications is greater than number of patients because four patients had more than one complication.

†Requiring intubation or medication intravenously.

tus was further defined by assignment to an American Society of Anesthesiologists physical status class (ASA classification) by the attending anesthesiologist (Table 1). This classification does not directly reflect the patient's actual anesthetic risk, but suggests relative risk based on the patient's overall physiologic condition.[1]

Surgical factors studied included length of surgery, level of training of the operating surgeon, and type of tube placed.

Factors relating to anesthesia included duration of anesthesia from the placement of the ventilation mask to the discontinuation of the anesthetic gases, including oxygen, the level of training of the anesthetist, and anesthetic medications given both preoperatively and intraoperatively. Patients were classified by ASA assignment and then divided into groups based on the type of complication: "none," "airway," and "other." Airway complications were divided into "mild" (readily treated with jaw thrust, positive pressure ventilation, or an oral airway) and "severe" (needing medication intravenously and/or intubation). Oral airways are not routinely used in this institution. Examples of other complications include vomiting and cardiac dysrhythmias.

RESULTS

No complications were seen in 423 (82.9%) patients. Isolated mild upper airway obstruction requiring intervention with an oral airway, jaw thrust, or positive pressure ventilation via mask occurred in 61 children (12.0%); 52 patients were classified as ASA 1 and 9 patients as ASA 2. None of the 6 patients classified as ASA 3 or ASA 4 had any airway (or other) complications. An oral airway was placed in 44 (86.0%) of these 61 children.

Severe airway obstruction, requiring medication intravenously and/or endotracheal intubation, was encountered in seven children (1.4%). Five had complicating medical problems; two had a history of reactive airway disease (one of whom also had cerebral palsy, hydrocephalus, and a concurrent URI); one patient had a recent episode of croup and a concurrent URI; one child had Down's syndrome and a history of obstructive sleep apnea; and one patient had a repaired bilateral cleft lip and palate. Five of the patients with severe airway obstruction were ASA 1 and two were ASA 2.

Twenty-three other complications were encountered in 22 patients (4.3%). These included intraoperative vomiting (n = 2), postoperative vomiting (n = 9), bradycardia (n = 6), premature ventricular complexes (n = 3), transient temperature elevation (n = 1), severe preoperative agitation (n = 1), and a fall from the transport stretcher in the recovery room (n = 1). Of these, 19 patients were categorized as ASA 1 and 3 as ASA 2.

Four patients had more than one complication: two patients had airway obstruction with bradycardia (one with Down's syndrome), one patient had airway obstruction with intraoperative vomiting, and one patient had bradycardia and postoperative vomiting. There were no deaths during this study. For a summary of the complications see Table 2.

Table 4.—Incidence of Complications in Patients With Upper Respiratory Tract Infections (URI)*

		No. (%)	
	N	Complications	No Complications
URI	100	19 (19)	81 (81)
No URI	410	68 (17)	342 (83)

*No significant difference.

Patient Factors

The mean age (±SD) of the children was 3.8 ± 3.1 years (range, 0 to 18.0 years). The mean age (±SD) of the patients experiencing airway complications (n = 64) was 3.1 ± 2.8 years compared with the patients experiencing other complications who averaged 6.9 ± 4.0 years ($P < .01$). The mean age (±SD) of the 11 children who vomited was 8.0 ± 3.0 years. When compared with 3.3 ± 3.1 years in patients with complications other than vomiting (n = 72), the age difference was significant ($P < .001$) (Table 3).

A URI was diagnosed in 101 children (20%): 19% of patients with no complications and 22% of patients with complications (Table 4).

In patients with chronic medical problems, 82.1% experienced no complications. This was not significantly different than the 83.2% of patients without chronic medical problems who experienced no complications. Airway and other complications were also similar in this group of patients. Children with Down's syndrome, however, had a

Table 5.—Complications in Relation to Chronic Medical History*

		No. (%)		
Chronic Medical Problem	**Total No.**	**None**	**Airway**	**Other**
Respiratory	**65**	56 (86)	7 (11)	2 (3)
Craniofacial	**41**	31 (76)	8 (20)	2 (5)
Down's syndrome	**7**	4 (57)	2 (29)	1 (14)
Neurologic†	**35**	26 (74)	8 (23)	1 (3)
Cardiac	**23**	18 (78)	2 (9)	3 (13)
Obstructive symptoms	**4**	2 (50)	0 (0)	2 (50)
Other‡	**6**	4 (67)	1 (17)	1 (17)

*Four patients had more than one complications; several patients had multiple chronic medical problems.

†Cerebral palsy, hydrocephalus, and seizures.

‡Hematologic disorders, diabetes, severe gastroesophageal reflux, turner's syndrome, malignant hyperthemia (family history), lead poisoning, laryngomalacia, and morbid obesity.

Table 6.—Complication Rate by Level of Training of Nurse Anesthetist

	No. (%)			
Group	**Student Nurse Anesthetist**	**Nurse Anesthetist**	**Resident/ Fellow**	**Attending Physician**
None	77 (18.4)	209 (50.0)	83 (19.9)	49 (11.8)
All complications*	28 (32.6)	32 (37.2)	18 (20.9)	8 (9.3)
Airway	23 (33.8)	26 (38.2)	12 (17.6)	7 (10.3)
Other	5 (27.8)	6 (33.3)	6 (33.3)	1 (5.6)
Total patients anesthetized	105 (20.8)	241 (47.8)	101 (20.0)	57 (11.3)

* χ^2 $P < .05$ when comparing the presence or absence of any complications suggestive of a relationship, although the correlation is low.

relatively greater rate of airway complications than the group as a whole, although this was not statistically significant (Table 5).

There was a history of exposure to general anesthesia in 178 patients (35.6%). Considering all patients who had a complication (n = 87), 40% had prior anesthesia exposure. However, of patients with complications other than airway, 68% had a history of anesthesia exposure ($P < .01$).

Surgical Factors

The duration of surgical manipulation was 4.8 ± 2.8 minutes. The mean ± SD duration of surgery for patients experiencing no complications was 4.6 ± 2.5 minutes compared with the duration of surgery for patients experiencing complications, which was 5.6 ± 3.9 minutes ($P < .05$). Residents performed 48.5% of the operations and 61.5% were performed by the attending otolaryngologist. There was a significant relationship ($P < .05$) between the level of training of the operating surgeon and the presence of complications, although this was weak (r = .101). There was no relationship between the type of tube placed and the presence of anesthetic complications.

Anesthesia Factors

The mean duration (±SD) of anesthesia was 1.8 minutes longer for patients experiencing any type of complication: 8.7 ± 3.1 minutes vs 10.5 ± 5.1 minutes ($P < .01$).

The experience of the anesthetist was related to the occurrence of complications (Table 6). Although student nurse anesthetists delivered the anesthesia to 20.8% of the children, they acted as the anesthetist for 33.8% of the children with airway complications. While 19% of the children received anesthesia from residents or fellows, 30% of nonairway complications were seen in their patients. Nurse anesthetists delivered anesthesia to 47.8% of the patients but accounted for only 37.2% of all complications. Knowing the level of the anesthetist gives some indication of whether or not there will be any complication ($P < .05$, $r = .139$). However, if the complications are categorized into airway vs other complications, this is not statistically significant ($P = .06$).

COMMENT

The benefits appear to outweigh the surgical risks of this frequently performed procedure. In adults and some older, cooperative children, tube placement may be performed with the patient awake using local anesthesia. Most children, however, cannot remain quiet for this procedure using a local anesthetic. In these patients, the surgical risks are therefore compounded by the anesthetic risks of the procedure.

In this study, the most frequent complication was mild upper airway obstruction (12.0%). During the administration of anesthesia by mask, airway control is usually the greatest concern. Inadequate control of the airway can cause changes in ventilation and oxygenation or can result in the introduction of air into the stomach. These factors may then contribute to other complications such as cardiac dysrhythmias and vomiting. Hypertension, a significant complication in a study by Diaz[2] of 313 infants undergoing orotracheal anesthesia for herniorrhaphy, was not encountered in this study of nonintubated children.

Vomiting occurred in 11 patients, 2 intraoperatively and 9 postoperatively, including 3 that occurred after discharge from the same-day surgery unit. The incidence of vomiting after discharge may actually be higher than reported because our data were dependent on parental information.

Halothane (Fluothane) inhalation anesthesia is used frequently in children. Its advantages are reduction of laryngeal reflexes and subsequent laryngospasm, decreased salivation, inhibition of bronchospasm and cough, smooth and rapid induction, and emergence without significant vomiting.[2,3] Halothane, however, has been reported to cause cardiac dysrhythmias in up to 34% of children who are less than 14 years old.[4] Infants have increased halothane requirements and also have exquisite sensitivity to halothane's myocardial depressant properties.[2] Cardiac dysrhythmias have been reported to occur with increased frequency and severity when

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atropine is administered preoperatively.[4]

All of our patients received preoperative atropine and most of them also received halothane. Tachydysrhythmias occurred only in 3 patients (0.6%), while bradycardia occurred in 6 patients (1.2%). Of the patients who had episodes of bradycardia, preoperative atropine had been given intramuscularly in four patients and orally in three patients. There did not appear to be an increased incidence of cardiac dysrhythmias in our patients compared with those studied by Thurlow.[4] This may be related to the anesthetic technique in our study that did not require endotracheal intubation.

The mean age of children experiencing nonairway complications (6.9 years) was significantly higher than in the group as a whole (3.8 years). Children older than 4 years were more often induced with a high nitrous oxide anesthetic gas mixture, which may have increased their incidence of vomiting.

The finding of an increased frequency of problems in children with a history of exposure to general anesthesia was not expected and is difficult to explain. Interestingly, one child had tympanotomy tubes placed in December 1987 and again in December 1988. On both occasions, he had multifocal premature ventricular complexes.

Tait and Knight[5] prospectively studied 489 children for the effect of a URI during bilateral myringotomy and tympanotomy tube placement under general anesthesia. They found that the prevalence of perioperative complications in children with URIs was similar to that in children without URIs. In this study, four of the seven patients with severe airway obstruction had a URI at the time of surgery. Two of these patients had chronic medical problems (Down's syndrome, cerebral palsy, and hydrocephalus). These data suggest that when a URI is present along with other chronic medical problems, the anesthesia risk may be higher. Otherwise, our data concur with Tait and Knight[5] suggesting that, in an otherwise healthy child, the presence of a URI is not a reason to cancel the procedure. However, in this study no child with an elevated temperature on the morning of surgery had the procedure performed.

The presence of chronic medical problems or higher ASA classification did not suggest an increased risk for perioperative anesthetic complications except in children with Down's syndrome; however, the numbers here are too small for definite conclusions to be made. The type of anesthetic complications do not appear to be directly related to the particular chronic medical problems.

The length of both surgery and anesthesia was only minimally increased (1 to 2 minutes) in patients with airway obstruction or other complications. This most likely reflects rapid recognition and treatment of these problems at the Children's Hospital of Buffalo.

The level of training of both the surgeon and the anesthetist appeared to be related to an increased rate of complications. Although one can explain the inexperience of using mask ventilation techniques by the anesthetist, it is more difficult to explain the relationship between the level of training of the operating surgeon and the incidence of anesthetic complications.

In 510 children undergoing bilateral tympanotomy tube placement under the described anesthetic regimen, 83% experienced no complications. Mild upper airway obstruction, vomiting, and cardiac dysrhythmias were the most commonly seen complications. All complications were successfully treated and did not result in significant or prolonged morbidity.

The presence of a URI in an otherwise healthy child does not appear to necessitate cancellation of surgery. The anesthesia given for the insertion of tympanotomy tubes appears to be safe; however, these data are limited to the setting of a children's hospital. Further multi-institutional study is required, in particular to determine the risk of this procedure for those children with severe medical problems.

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Three-Dimensional Images of the Temporal Bone and Experimental Otitis Media in Japanese Monkeys

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• Since the middle ear structure of animals commonly used for experimental study is different from that of humans, we used the Japanese monkey (*Macacus fuscatus*) as an animal model for otitis media with effusion (OME). The exact similarities and differences of the ear structure between humans and Japanese monkeys were studied by the use of computer-aided three-dimensional reconstruction, in addition to light and electron microscopy. Otitis media with effusion was repeatedly induced by direct intratympanic inoculation of one of the following: keyhole limpet hemocyanin; following systemic immunization with keyhole limpet hemocyanin, *Streptococcus pneumoniae*; or endotoxin. The temporal bones were serially sliced with a diamond band saw, after which the histologic findings were examined by light and electron microscopy on the basis of macroscopic observations. Each substance induced OME equally, 2 to 3 days after inoculation. Inflammatory reaction of the middle ear mucosa extended to all of the air cells; subsequently, the inflamed mucosa returned to normal in each case along with normalization of both the tympanometric and otoscopic findings. No remarkable architectural change remained, even after OME was induced repeatedly. These findings are applicable to acute otitis media and acute mastoiditis. The development of chronic middle ear effusion was not observed in this study. The usefulness of the diamond band saw and computer-aided analysis for temporal bone histologic evaluations is emphasized.

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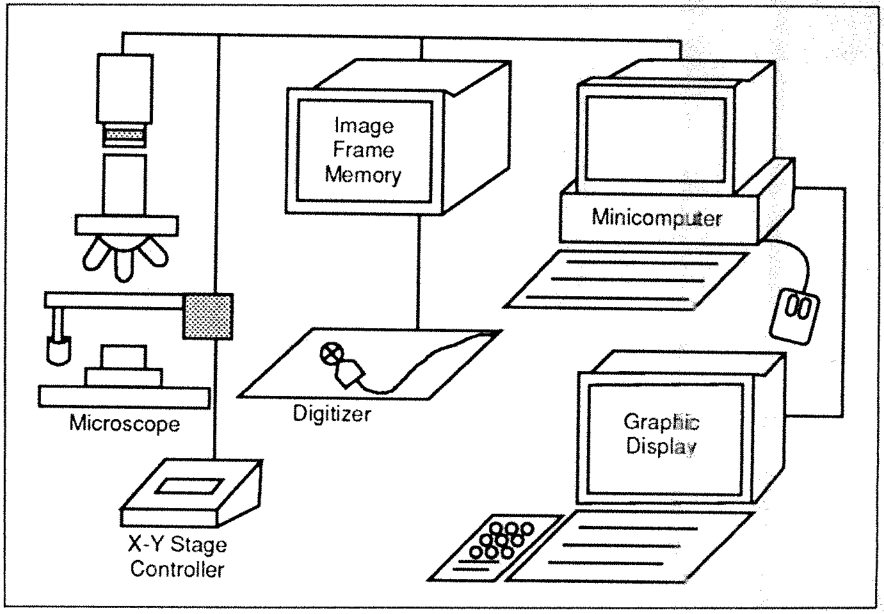
Morphologic changes occurring in the middle ear mucosa in otitis media with effusion (OME) have been clarified by use of numerous animal models.[1] In studies of experimental OME, an ideal animal model is one that is considered to have the following characteristics: that the animal itself not be too large; that the auditory capabilities of the animal be similar to those of humans; that the animal should not be susceptible to natural middle ear infections; and that the animal have a large middle ear cavity. The human middle ear is contiguous anteriorly to the eustachian tube and posteriorly to the complex mastoid air cells. These anatomic divisions relate to many clinical lesions. Until recently, chinchillas, guinea pigs, and rats have been the most commonly used animal models. However, since

Fig 1.—Block diagram of three-dimensional reconstruction computer system.



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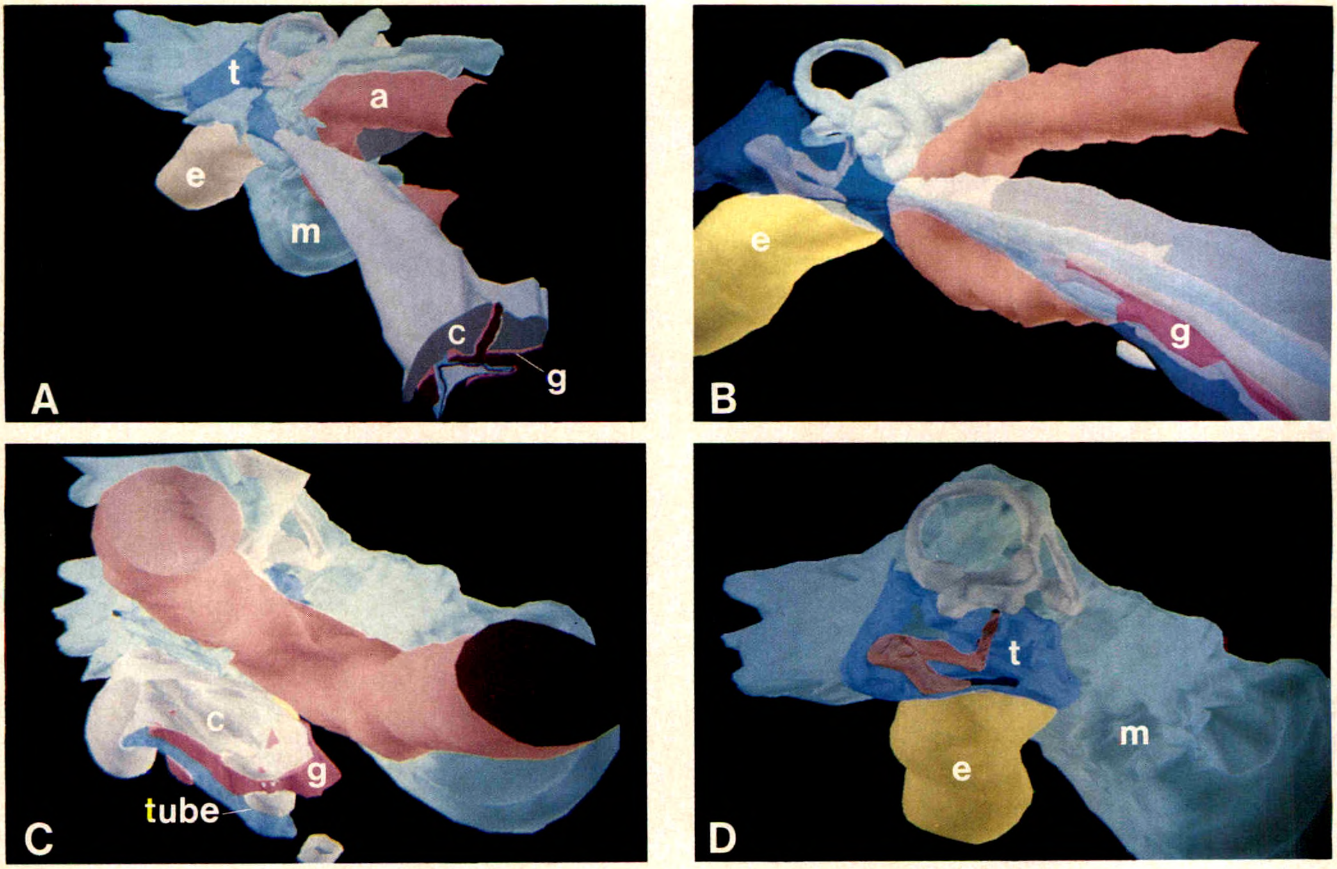

Fig 2.—Three-dimensional reconstructed images of the temporal bone of the right human ear. Panel A is the solid model; panel B, the transparent model; and panels C and D, the cut surfaces of the solid model. Lower case letters in panels have the following meaning: a, internal carotid artery; c, tubal cartilage; e, external auditory canal; g, distribution of the gland; m, mastoid air cells; and t, tympanum.

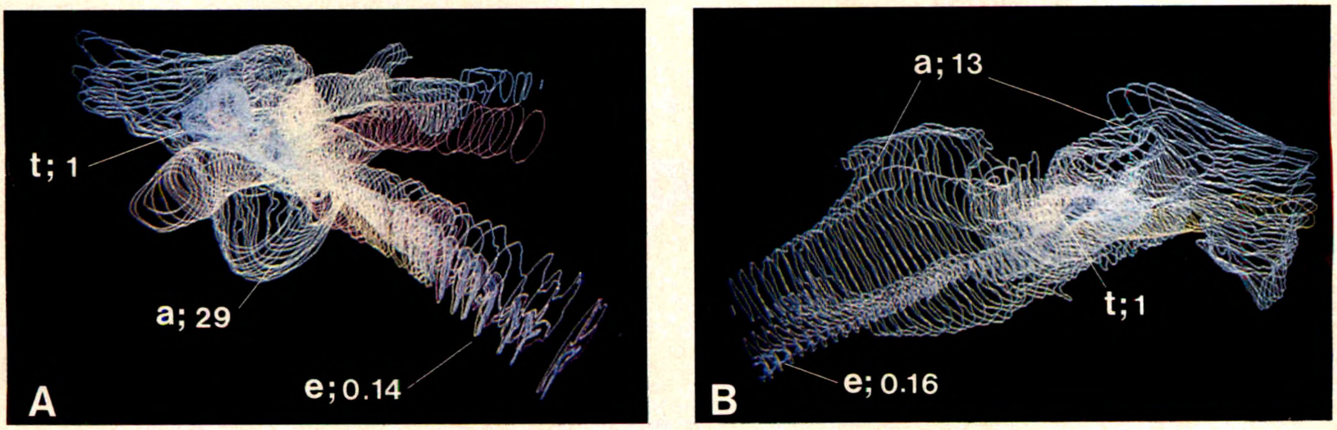

Fig 3.—Wire-frame models from the temporal bone of the left ear of a Japanese monkey. The volume-ratio differences of tubotympanum and air cell systems in both the human and the monkey are indicated in each picture by numbers. Lower case letters in panels have the following meaning: a, air cells; e, eustachian tube; and t, tympanum.

the ear structure of these animals is not identical to that of humans, otitis media and its sequelae in animals and humans cannot be compared easily. We experimented with the Japanese monkey (*Macacus fuscatus*) as an animal model for OME. Although the ear structure of this animal is presumed to be less different from humans, compared with other animals, experimental OME in the Japanese monkey has not been studied. To determine whether or not the Japanese monkey is an ideal animal model for OME, the exact similarities and differences of the ear structure between humans and Japanese monkeys were studied, after which OME was induced experimen-

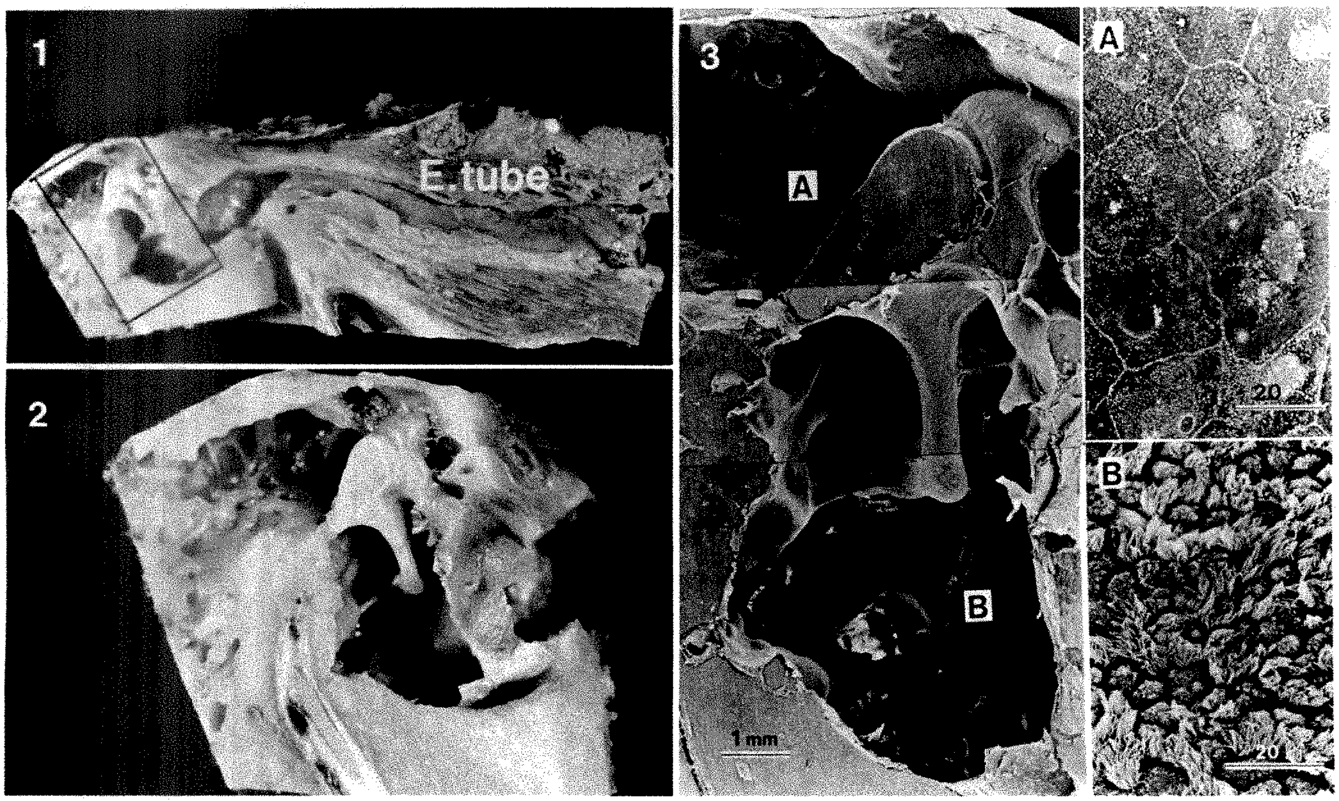

Fig 4.—A normal human middle ear. Panels 1 and 2 show a macroscopic view of the tubotympanum dissected with a diamond band saw. Panel 3 shows a scanning electron microscopic observation of the rectangle in panel 1 (×9). At far right, scanning electron photomicrographs A (×600) and B (×700) correspond to the high-magnification view of the sites marked A and B in panel 3, indicating the distribution pattern of nonciliated and ciliated epithelium. Unit of measurement of the bar is the micrometer.

tally. For the morphologic observations in this study, we used a computer-aided three-dimensional reconstruction, in addition to light and electron microscopy.

MATERIALS AND METHODS

Comparison of the Normal Ear Structure of Humans and Japanese Monkeys

Three-dimensional Reconstruction of the Temporal Bone.—Temporal bones, which were taken from a 47-year-old man free from ear diseases and from a normal adult Japanese monkey, were used. To obtain histologic sections for three-dimensional reconstruction, undecalcified temporal bones were immersed in 10% formaldehyde or in Karnovsky's fixative (2.5% glutaraldehyde and 2% paraformaldehyde in 0.2 mol/L of cacodylate buffer; pH, 7.4), dehydrated, embedded in polyester resin (Rigolac, Maruto Ltd, Tokyo, Japan), and sliced with a diamond band saw (Exakt sawing machine, Exakt Apparatebau, Norderstedt, West Germany) as follows: (1) a microscope slide was attached to each opposite surface of the embedded block by cyanoacrylate adhesives (Loctite Holdings Ltd, Welwyn Garden City, England); (2) one of the two slides attached to the block was held onto the vacuum plate of the machine; and (3) the other slide attached to the opposite side of the block was cut off, together with a section of mounted temporal bone, by sawing. This method produced semiserial sections attached to the microscope slides at a minimum interval of 450 μm. The minimum thickness of the sections was about 100 μm, which was calculated by subtracting the cutting loss of about 350 μm. All sections were stained with toluidine blue O. Ninety sections from the bone from the human and 68 sections from the bone from the Japanese monkey were used for three-dimensional recontruction. Before attaching microscope slides to the block, some reference marks were put on its surface by use of the diamond band saw, such that the mark fell at right angles to the cutting surface. These marks were used as a coordinate for each section when data on the structure were entered into the computer. Figure 1 shows the block diagram of the computer system. Microscopic images, which were entered into an image-frame memory (Nexus 6800, Kashiwagi Research Corp, Tokyo, Japan) from a microscope through a television camera, were traced with a digitizer. All fields of microscopic vision on a slice were able to be traced continuously, because the microscope X-Y stage holding the slide was controlled by a computer (microscanner controller, Sapporo Breweries Ltd, Tokyo, Japan) that was connected to the image-frame memory. Data were then sent to a minicomputer (Sun 4, Sun Microsystems Inc, Mountain View, Calif) in which a three-dimensional structure was built up by software (TRI, Ratoc System Engineering Inc, Tokyo, Japan). The reconstructed images were shown in perspective on a graphic display (GR 4416, Seiko Electronics Inc, Tokyo, Japan).

Tissue Preparation From Temporal Bones for Macroscopic and Microscopic Observations.—Six temporal bones from the human and 29 temporal bones from the Japanese monkey, which were fixed with 10% formaldehyde or Karnovsky's fixative, were serially sliced with a diamond band saw at a minimum interval of 1 mm. Histologic preparations then proceeded, following the macroscopic observations of the slice. For light microscopy, slices were decalcified with 10% ethylenediaminetetraacetic acid

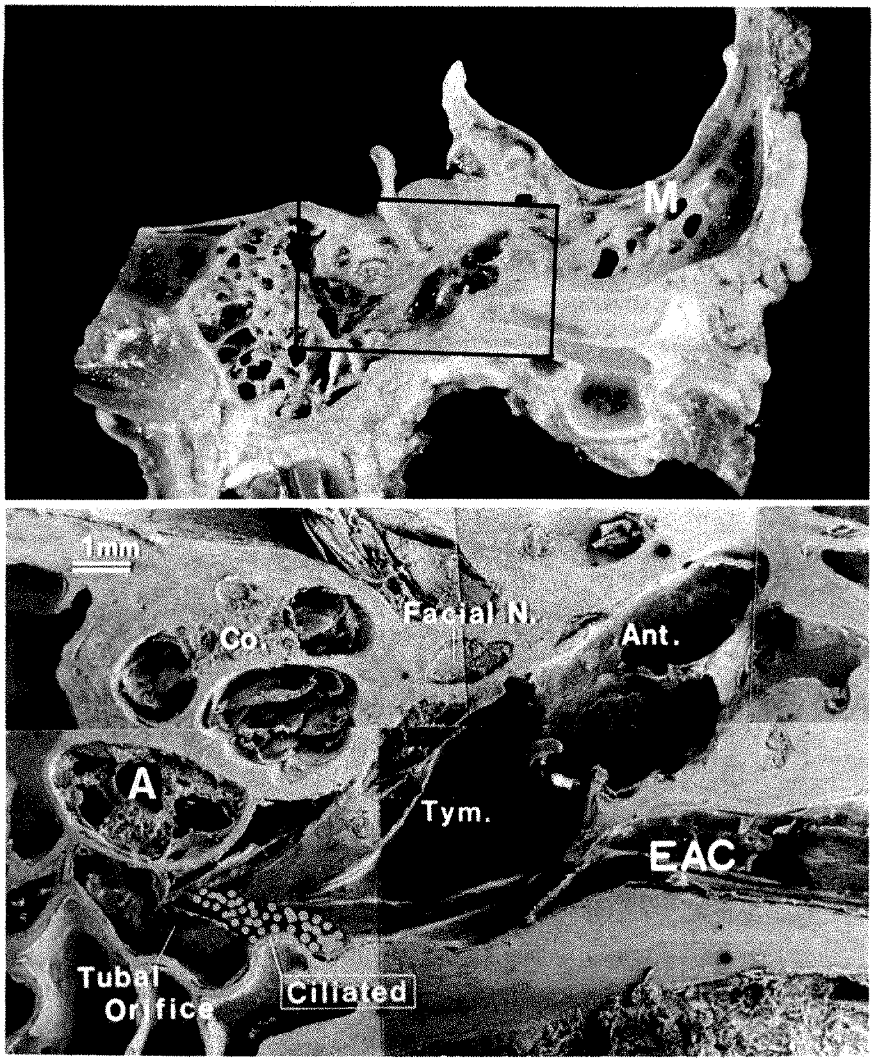

Fig 5.—At top, temporal bone from the left ear of a Japanese monkey. At bottom, scanning electron photomicrograph (X8) of the area enclosed by the rectangle in the panel above, indicating the distribution pattern of ciliated and nonciliated epithelium in the tympanum. A ciliated epithelium is located only near the tubal orifice contiguous to the eustachian tube. M indicates mastoid air cells; Tym, tympanum; Ant, antrum; EAC, external auditory canal; Co, cochlea; A, internal carotid artery; and Facial N, facial nerve.

in 0.1 mol/L of TRIS buffer (pH, 6.95) and embedded in paraffin or glycol methacrylate (JB-4, Polysciences, Warrington, Pa). Sections of 4 to 8 μm in thickness were stained with hematoxylin-eosin. For transmission electron microscopy, several pieces of mucosa were stripped from the bony wall of the slices under an operative microscope, postfixed in buffered 2% osmium tetroxide, dehydrated through graded concentrations of ethanol, and embedded in epoxy resin (Epon). Thin sections were stained with uranyl acetate-lead citrate. Observations were made with a transmission electron microscope (JEM-100C, Jeol, Tokyo, Japan). For scanning electron microscopy, the slices were trimmed to a square, each side of which was approximately 2 cm, postfixed in buffered 2% osmium tetroxide, dehydrated, and dried by the critical-point method. The specimen was coated with gold and examined with a scanning electron microscope (JSM-25A, Jeol).

Experimental Otitis Media in Japanese Monkeys

Induction of Otitis Media.—Thirteen healthy wild Japanese monkeys, weighing 5 to 8.5 kg and free of middle ear infection, were used. Monkeys were anesthetized by percutaneous injection of ketamine hydrochloride before every maneuver. Over a period of 8 months, otitis media was induced repeatedly 66 times in 22 ears (from 1 to 9 times, for an average of 3 times in the same ear) by direct intratympanic inoculation of the following substances: (1) 34 times with 300 μg of keyhole limpet hemocyanin in 150 μL of phosphate-buffered saline plus 150 μL of 0.8% hydroxypropyl cellulose 3 weeks after systemic immunization by intradermal injection of 3 mg of keyhole limpet hemocyanin in complete Freund's adjuvant; (2) 17 times with 10^8 colony-forming units of *Streptococcus pneumoniae* (type 19) in 0.2 mL of phosphate-buffered saline; and (3) 15 times with 0.5 to 1.2 mg of endotoxin (Meiji Seika Kaisha Ltd, Tokyo, Japan) obtained from nontypable *Haemophilus influenzae* in 500 μL of phosphate-buffered saline. The middle ears were monitored by tympanometry and microscopic observation of eardrums every second to third day. Middle ear effusion was examined by aspiration through the eardrum using a 23-gauge needle. The sequential inoculation or systemic immunization following the earlier induction of otitis media was performed after both the tympanogram and otoscopic findings normalized. The other 4 (of 22) ears served as controls.

Histopathologic Examination.—Each temporal bone was removed during the natural course of otitis media so as to examine the histologic changes of the mucosa, both during and after the disease. The temporal bones were serially sliced with a diamond band saw at an interval of 1 to 2 mm after several days' immersion with Karnovsky's fixative. Using the preceding methods, observations were made using light, transmission electron, and scanning electron microscopy.

RESULTS

Architectural Similarities and Differences of the Normal Ear of Humans and Japanese Monkeys

Figures 2 and 3 show various computer images of the component parts of the temporal bone from both the human and the Japanese monkey. Using a wire-frame model, a solid model, a transparent model, and a function that rotates and cuts the image in any desired direction instantaneously, the spatially complex structure of the temporal bone was easily observed. Unlike the human ear, the Japanese monkey ear had extended peritubal and pericarotid air cells, in contrast with mastoid air cells. The volume of tubotympanum and air cells, calculated by this computer system, revealed the ratio of the size of one compartment to that of another, for both the human and the monkey. As shown by the numbers in Fig 3, the air cell system, compared with the tympanum, was smaller in the monkey than in the human.

Histologic examinations of human and monkey temporal bones demon-

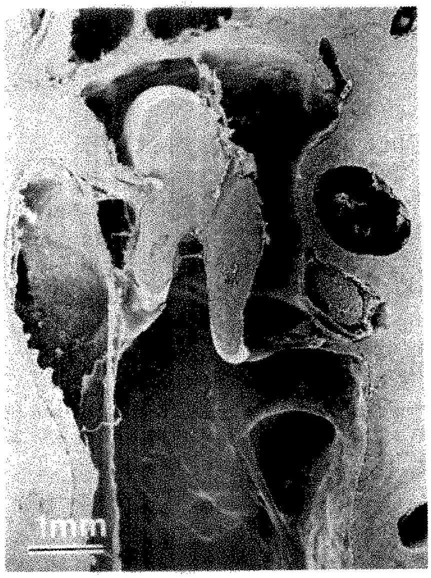

Fig 6.—Scanning electron photomicrograph of the tympanum of the left ear of the Japanese monkey. The largest part of the tympanum is covered by nonciliated epithelial cells (×10).

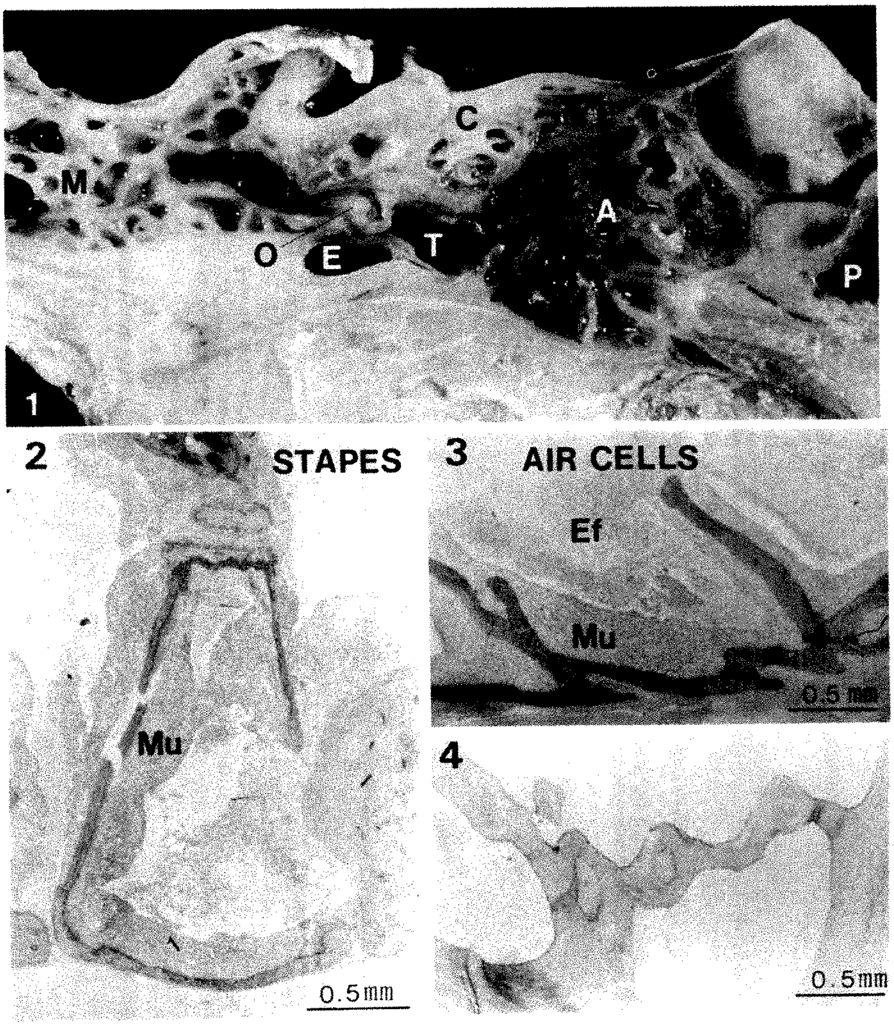

Fig 7.—Panel 1, a 1.5-mm-thick slice of the right temporal bone of a Japanese monkey with otitis media with effusion. Note the fluid accumulated in all of the air cells as well as in the space around the ear ossicles. In panels 2 (hematoxylin-eosin, ×27) and 3 (hematoxylin-eosin, ×23), the thinnest mucosa, such as that of the ear ossicles and the air cells, thickens and is infiltrated by inflammatory cells. Panel 4 (×23) shows a normal control air cell. A indicates peritubal and pericarotid air cells; C, cochlea; E, external auditory canal; M, mastoid air cells; O, ear ossicles; P, pharynx; T, tympanum; Mu, mucosa (thickened); and Ef, effusion.

strated the characteristic distribution of ciliated and nonciliated epithelium covering the mucosa of the middle ear. Figure 4 shows a human ear dissected with a diamond band saw. As is well known,[2] a ciliated epithelium, interspersing secretory cells among ciliated cells, covers the promontory in continuity with the eustachian tube, whereas the ciliated epithelium transforms into a flat squamous epithelium on the peripheral side of the facial nerve torus. However, in Japanese monkeys a ciliated epithelium containing secretory cells was located only in a small part of the mucosa as follows: near the tubal orifice of the tympanum contiguous to the eustachian tube (Fig 5). The largest part of the tympanum (Fig 6) was covered by flat squamous epithelial cells with a few microvilli on the apical surface.

Experimental Otitis Media in Japanese Monkeys

Incidence of Otitis Media and Its Natural Course.—Each substance induced otitis media a total of 34 times (52%) with retention of a serumlike fluid 2 to 3 days after its intratympanic inoculation. The tympanogram indicated type B, corresponding to OME, then type As, and, finally, type A, 7 to 10 days later. Otitis media with aural discharge, seen a total of 8 times (12%), evolved into OME and also healed in the same manner 2 to 3 weeks later. No perforation of the eardrum remained. The other 24 times (36%) merely indicated a type As or type A tympanogram after inoculation.

Morphologic Changes in OME.—The OME induced by each of the three substances was similar under microscopic observation. The most remarkable finding in OME was that the inflammation extended to all of the air cells within several days. Figure 7 shows the findings of a temporal bone slice affected by OME 3 days after inoculation, as well as its light microscopic observation. Accumulated fluid is seen in all air cells, as well as in the tympanum. Under light microscopic observation, even the thinnest mucosa, such as that of the air cell and the ear ossicles, thickened remarkably and was infiltrated by numerous inflammatory cells. Scanning and transmission electron microscopic observations of OME revealed changes in each type of epithelium. In the specimen shown in Fig 8, panel A, the space around the ear ossicles is occupied by fluid. Microvilli of nonciliated cells are lengthened everywhere, and secretory cells contain numerous granules (Fig 8, panels B through D). In the mucosa near the tubal orifice of the tympanum (Fig 9, panel A), polymorphonuclear cells have infiltrated into the middle ear cavity through the epithelial layer.

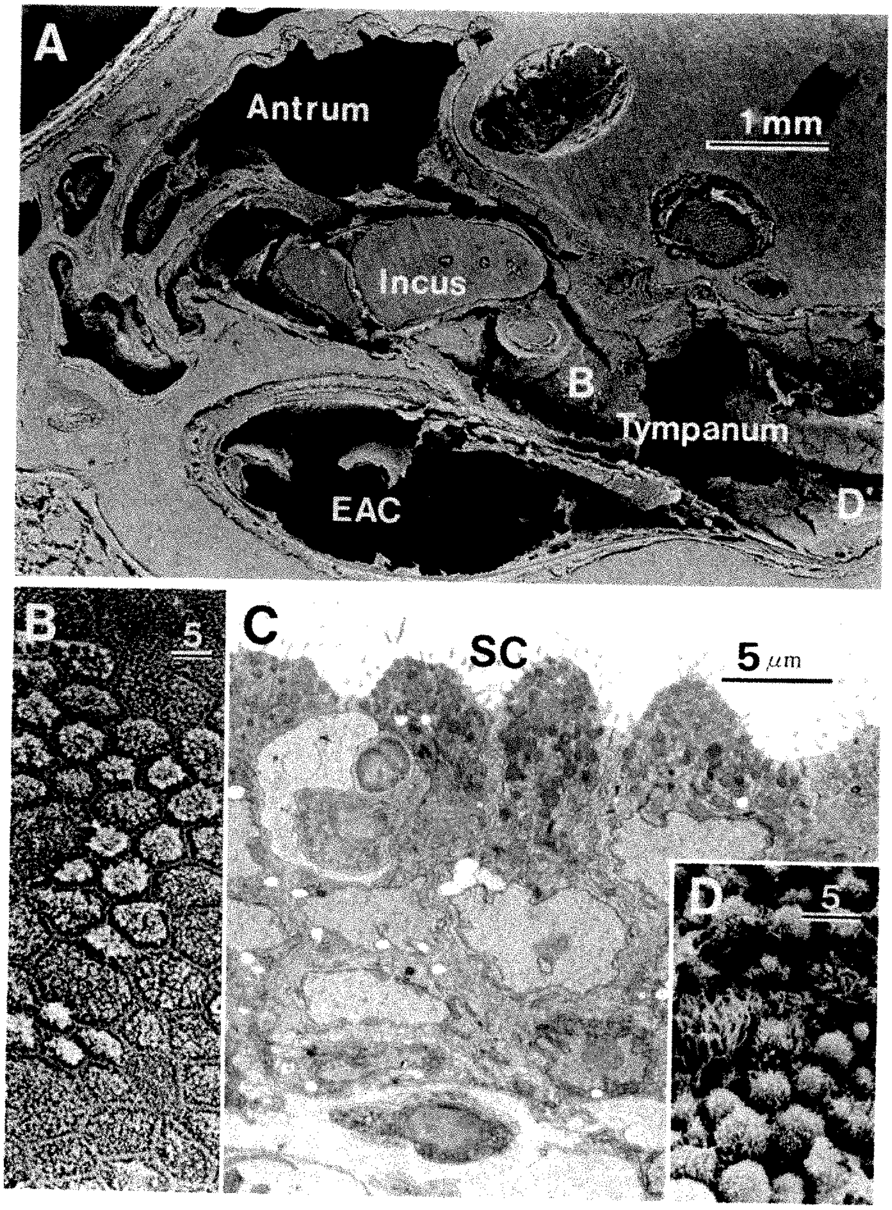

Fig 8.—Scanning electron (SEM) and transmission electron (TEM) photomicrographs of the tympanum of a Japanese monkey affected by otitis media with effusion. Panel A shows a low-magnification (×16) SEM of the tympanum. Panels B and D show high-magnification SEMs (panel B, ×1200; panel D, ×1600) corresponding to each site in panel A. Microvilli of nonciliated cells are lengthened, and secretory cells near the tubal orifice of the tympanum (panel C, TEM; ×2900) contain numerous granules. EAC indicates external auditory canal; SC, secretory cell. Unit of measurement of the bars in panels B and C is the micrometer.

The lamina propria of the mastoid antrum mucosa contains many fibroblasts, suggesting the acceleration of fibrosis. Erythrocytes, outside of the capillary due to transudatory hemorrhage, are assumed to exude together with serum into the middle ear cavity (Fig 9, panel B). Such changes were observed also in the osseous portion of the eustachian tube, while little change was seen in the cartilaginous portion of the eustachian tube. The inflammatory reaction in otitis media induced repeatedly was not remarkably distinct from that in otitis media when it was first induced. When the tympanogram pattern shifted to type A from type B 7 days after the inoculation, the inflamed mucosa had already returned to normal, except for slightly lengthened microvilli, even in the most frequent case of otitis media induced repeatedly. No architectural change remained.

COMMENT

The structural similarities between the ears of humans and Japanese monkeys provided a better evaluation of some defense mechanisms in the middle ear. In the human ear, anatomic isthmi, namely, the tubal isthmus and tympanic isthmus, are thought to protect mechanically against the influx of foreign substances from the nasopharynx. In addition, the respiratory-type epithelium of the middle ear acts as a biological defense. However, this type of epithelium sequentially transforms into a flat squamous epithelium as the distance from the tubal isthmus increases. This finding suggests that the peripheral portion of the middle ear cavity is rarely exposed to foreign substances under normal conditions. Although some architectural differences between the ears of humans and Japanese monkeys were clarified in this study, note that the differences in ear architecture are fewer than those between humans and other animals. Variations in the ear structure of Japanese monkeys were very few, possibly due to their rare susceptibility to natural middle ear infections. On the basis of these findings, we were able to observe otitis media experimentally in Japanese monkeys and compare it with that seen clinically in humans. The most important method in this study was the systematic morphologic examination, observing the temporal bone macroscopically and then using light, transmission, and scanning electron microscopy. Although the temporal bone in Japanese monkeys is as hard as it is in humans, we successfully used a diamond band saw for morphologic procedures.

For computer-aided three-dimensional reconstruction, this method produced semiserial sections at a minimum interval of 450 μm from an undecalcified temporal bone embedded in polyester resin, each section being given precise reference marks, which were the most important key when data on the structure were entered into the computer. Although several authors reported three-dimensional reconstruction of the temporal bone from celloidin-embedded sections,[3-4] whole temporal bone reconstruction was first achieved by the present technique; consequently, a quantitative

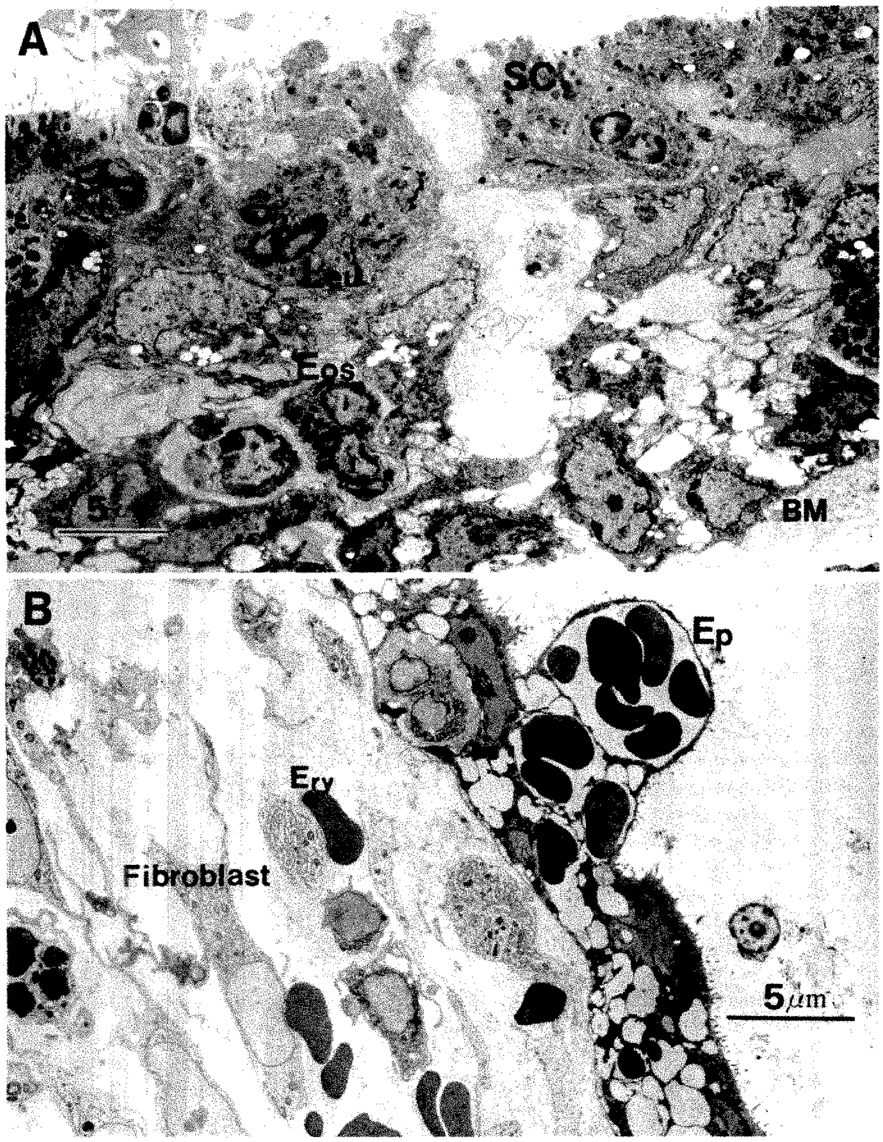

Fig 9.—Transmission electron photomicrographs of the mucosa near the tubal orifice of the tympanum (panel A [×2800]) and in the mastoid antrum (panel B [×3300]) affected by otitis media with effusion in the Japanese monkey. Various inflammatory reactions are seen as mentioned in the "Results" section. Leu indicates leukocyte; Eos, eosinophil; BM, basement membrane; SC, secretory cell; Ep, epithelium; and Ery, erythrocyte.

comparison between the ear architecture of Japanese monkeys and humans was able to be made. The cutting interval of 450 μm was sufficient, but could only be used to reconstruct semimicroscopic images. Thinner, serially cut sections are necessary to observe finer images.

Serial slices (1-mm thick), obtained from preembedded temporal bones by means of a diamond band saw, retained their fine structure. On the basis of macroscopic findings, scanning and transmission electron microscopic observations, as well as light microscopic observations, were made systematically. Intratympanic inoculation of keyhole limpet hemocyanin following systemic immunization, *S pneumoniae*, or endotoxin is a previously reported method of inducing OME in other animals.[5-7] The most important result of inducing OME in the Japanese monkey was that all sites of mucosa, even in peripheral air cells, were able to become inflammed readily, resulting in the accumulation within several days of effusion up to the air cells. According to otoscopic and tympanometric findings, the natural course of otitis media induced experimentally in Japanese monkeys was similar to acute otitis media in humans. The effusion may consist of exudation from capillaries and fluid from secretory cells. Although lengthened microvilli probably contributed to absorption of the fluid, tympanic and tubal isthmi promoted the retention of fluid. However, in the present study the inflammation in all sites healed 10 to 20 days after inoculation. Fluid retention, as well as architectural changes, were not found even in cases of otitis media induced repeatedly.

In conclusion, this study is applicable only to acute otitis media and acute mastoiditis in humans. We were unable to observe the development of chronic middle ear effusion or chronic otitis media. It was found that the Japanese monkeys used in this study had considerable resistance to diseases, both locally and systemically, possibly because they were raised under natural selection. The implication of the characteristic distribution pattern of a ciliated epithelium in the Japanese monkey is unclear at present. Because of the architectural similarities between the ears of humans and Japanese monkeys, further studies are worthwhile. The diamond band saw and computer-aided analysis for histologic investigations of the temporal bone should prove to be useful in future studies.

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Blood Viscosity and Sensorineural Hearing Loss

Minka Hildesheimer, PhD; Fani Bloch, MA; Chava Muchnik, PhD; Moshe Rubinstein, MD†

• Two groups of 33 subjects each, one experimental and one control, matched one-to-one for age and occupation, were chosen from a large number of subjects who were covered by special insurance for annual medical control at our hospital. The periodical checkups included cardiovascular, nervous, and renal systems, as well as vision and hearing. In addition routine blood tests, including whole blood viscosity, were also performed. The experimental group consisted of subjects in whom a bilateral, slight, and unexplained sensorineural loss of hearing was detected in the routine audiological testing, without any known reason. In the control group, the routine hearing tests demonstrated normal hearing. The differences between the two groups were statistically significant in pure-tone threshold level and in speech discrimination score, when the test was performed at a −5-dB signal-to-noise ratio. The results of the vestibular tests were normal in both groups. Hematocrit and whole blood viscosity were slightly but significantly higher in the experimental group if compared with the control group. The number of subjects with abnormal whole blood viscosity results was higher in the experimental group. The whole blood viscosity as the etiological factor responsible for the hearing deterioration is described.

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The cause and effect relationship between disorders in blood circulation and an eventual development of hearing damage is not always evident, at least not at the beginning of the pathological process. The dependence of the normal ear function on a continuous and satisfactory blood supply is well known and generally accepted. A chronic deficit in the labyrinthine blood supply is usually explained by failure of many factors, but a failure of one factor only could probably occur at the initial stage of the pathological process. With time, additional etiological factors develop and the diagnosis becomes more arduous. It is the multiplicity of these factors that make it difficult, in a specific case, to produce convincing evidence of the initial ischemic nature of the inner ear damage.

In recent studies it was pointed out that increased blood viscosity may have a deleterious effect on hearing,[1,2] and Rubinstein et al[3] also elaborated on the involvement of the blood viscosity factor in chronic labyrinthine ischemia.

The therapeutic importance that can be achieved by lowering blood viscosity was demonstrated on brain circulation.[4] Lowering the hematocrit from 0.53 to 0.45 was associated with a 30% decrease in viscosity and a 75% increase in cerebral blood flow.

In chronic inner ear disease, medical efforts should be directed at a correct diagnosis in the shortest possible time, as only in this way can one arrest the progressiveness of the pathological process at a time when the labyrinth is only slightly damaged.

From the etiological factors that induce increased blood viscosity, a high hematocrit seems to be the most inoffensive, the reason being that the decrease in the flow of blood due to the hyperviscosity is already compensated by an increase in the capacity for carrying oxygen. Despite this, after phlebotomy in a patient with polycythemia vera, Davis and Nilo[5] attributed the improvement in hearing to the decreased blood viscosity.

In this study, an attempt was made to trace the sensorineural hearing loss at its beginning in a small group of subjects who showed a slight symmetrical and possibly progressive loss of hearing. At this initial stage of hearing loss, the high blood viscosity was studied as the etiological factor re-

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sponsible for the process of hearing deterioration.

SUBJECTS, MATERIALS, AND METHODS

Two groups were chosen from a large population, which, through special health insurance, has for many years been under permanent annual medical control in our hospital. Their regular checkup included cardiovascular, nervous, and renal systems, as well as vision and hearing. The routine blood tests included whole blood viscosity tests as well.

This population comes to our clinic two to three times weekly, and consists of three subjects at a time. A 6-month period was required for the selection of the experimental and control groups from the subjects who appeared at the clinic.

Each group constituted 33 male subjects, matched one-to-one in age and occupation. The subjects in both groups were, at the time of this study, symptom free with no general or local conditions that could affect hearing. Their age ranged between 37 and 64 years, with an average of 59 years.

The experimental group constituted subjects in whom a slight bilateral and unexplained sensorineural loss of hearing was detected in the routine audiological testing. Any general condition that could affect hearing loss was excluded, eg, a subject who was previously checked for hypertension was not included. Any local condition that could induce hearing loss was excluded as well, ie, noise exposure at work or in army service, or past complaints of unsteadiness or tinnitus. Any past complaint of hearing difficulties were excluded as well. Fifty experimental subjects were collected on the basis of these criteria.

The control group was chosen from the same large population, but the criteria were normality in all aspects of health and normal hearing. The aim was to match 50 subjects with 50 of the experimental group, but only 33 were cooperative by wanting to give their time to further testing, and exactly matched 33 of the experimental group in age and occupation. Thus, the final groups consisted of 33 subjects each.

This population was cooperative but, due to their inability to devote much time, our investigation was limited to a minimal battery of measurements. The hearing was evaluated according to the results of pure-tone audiometry, speech reception threshold, speech discrimination tests done using phonetically balanced monosyllabic words, and speech discrimination using the phonetically balanced words with competing white noise at a signal-to-noise ratio of 0 and −5 dB. Evaluation of the vestibular system was done by using electronystagmography and included calibration of the instrument and the biological response of the subjects (to 10° of eye rotation for 1 cm of displacement of the recording paper). By this, eventual overshooting or undershooting can be objectivated. Spontaneous and positional nystagmus was recorded.

Labyrinthine response to angular acceleration followed and was performed on a nystagmograph (Alvar Giro, type P), which included prerotatoric recordings of the nystagmus to acceleration of $1°/s^2$ and postrotatoric recordings after a sudden halt of a uniform rotation of $90°/s^2$.

On the day of the hearing and vestibular test, a fasting whole blood viscosity test was performed on a microviscometer (Brookfield Engineering Laboratories, Stoughton, Mass). The blood sample needed was small, 1.2 mL of blood anticoagulated with dry edetic acid (1.5 mg/mL). The viscosity was measured at eight shear rates from $1.15\ s^{-1}$ to $230\ s^{-1}$ at 37°C.

From the same blood sample the blood hematocrit was measured manually using a microhematocrit method.

RESULTS

The criteria for normal hearing used in this study were the hearing results for different age groups.[6] To compensate for the SDs that are not available, an additional 15-dB loss in the frequency range of 250 to 4000 Hz and 20 dB in 6 and 8 kHz were still considered as normal for age. All the subjects in the control group followed these criteria, each according to his age group. No one had any complaint associated with hearing or the ear.

In all subjects in the experimental group, the hearing threshold results were higher than the level set by the criteria in one or more tested frequencies but, as mentioned, without any known reason that could induce or influence that hearing loss. The comparison between the results of the experimental and control groups was done using a paired *t* test. The pure tone threshold results are presented in Table 1 and in the Figure. The figures are the result of air-conduction audiometry. Subjects with air-bone gaps were excluded. There was a significant difference beween the groups in all tested frequencies ($P < .05$). However, the hearing loss was greater at the higher frequency.

The speech reception threshold in the experimental group was 13.5 dB (SD, 7.95), while in the control group it was 8.7 dB (SD, 4.26). Both results are within normal range, but the difference was statistically significant (paired *t* test, $P < .05$).

In the speech discrimination test, the results obtained were similar in both groups, ie, 97.5% in the experimental group and 98.8% in the control group. Significantly different results ($P < .05$) were obtained when speech discrimination was tested at a signal-to-noise ratio of −5 dB. In the experimental group only 7.4% had a normal score of 70% (according to norms of advanced age in our clinic) and the remaining 92.6% had lower than normal scores. In the control group, 41.7% had normal results, while 58.3% had abnormal results (by corrected χ^2 test, $P < .05$).

Vestibular test results were normal in 79.3% of the experimental group and in 87.5% of the control group. Only slight asymmetry appeared between the nystagmus recordings to the right and left rotation sides in the remaining 20.7% of the experimental group and in 12.5% of the control group, the difference between the groups being insignificant.

Whole blood viscosity and hematocrit were tested on the same day as hearing and vestibular function. Mean hematocrit values were 0.45 in the control group and 0.473 in the experimental group, the difference being only 0.021, but statistically significant (paired *t* test, $P < .005$).

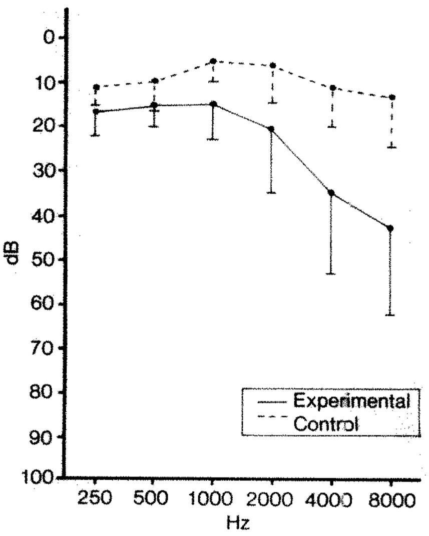
Results of blood viscosity were higher in the experimental group in all eight shear rates tested as compared with the control subjects, but statistically significant only in the six higher shear rates. The results are presented in Table 2.

The viscosity results were further evaluated by determining the number of subjects who had high viscosity in each group compared with the normal values established in our laboratory (average of 100 normal healthy people, age 20 to 65 years old). High viscosity was considered if at least in four shear rates the viscosity results were higher than the normal plus a range of 2 SDs.

According to this, in the experimental group the viscosity was higher than normal in 15 subjects. In the remain-

Table 1.—Average Hearing Loss in Pure-Tone Audiometry

		Group			
		Experimental		Control	
Frequency, Hz	Ear	Mean, dB	SD	Mean, dB	SD
250	R	15	6.43	10	6.25
	L	17.7	6.26	12.9	4.68
500	R	13.5	6.79	9.4	5.12
	L	14	6.47	10.6	5.7
1000	R	13.8	9.19	6.2	5.01
	L	14.2	8.85	7.4	4.86
2000	R	21.2	17.5	7	6.24
	L	21.2	13.29	8.8	5.73
4000	R	32.2	19.6	9.7	9.52
	L	37.4	18	11.8	9.51
8000	R	38.3	19.35	12	11.52
	L	47.5	21.45	14.6	12.21



Mean pure-tone curves and one-sided SDs of the two groups. The curves represent the average of right and left ears of the subjects.

ing 18 subjects the viscosity was within normal values, while in the control group in only 2 subjects was it higher than the normal values, the difference being significant (corrected χ^2 test, $P < .05$) (Table 3).

No correlation was found between the hematocrit and the viscosity. By corrected χ^2 test, a correlation between high blood viscosity and hearing loss in pure tone was found in the individual subjects ($P < .001$). By the same test significant dependence was found between high blood viscosity and lower than normal results in speech discrimination tested at a signal-to-noise ratio of -5 ($P < .05$).

COMMENT

The overabundant sensitivity of the ear may compensate for slight losses in hearing, rendering a patient symptom free despite a slight rise in his hearing threshold. In a progressive process, when a patient complains of hearing difficulties, usually a significant hearing loss affecting his verbal communication is already present. At this advanced stage, however, establishing the connection with a specific etiological factor, especially in cases of cardiovascular disturbances, is not an easy task. Even if, at the beginning of the pathological process, one specific etiological factor has started its noxious activity, with time other factors related to or as a result of the first one may appear and identification of the initial factor may become difficult. Under these circumstances of "multiple organ failure,"[7] different systems may contribute to the increase of cochlea damage.

A trial was done in this study to trace the hearing loss as it appears at the very beginning, assuming that slight but chronic deviations from normal in the blood supply to the cochlea can cause progressive and gradual hearing loss.

As mentioned previously, the experimental group in this study consisted of 33 healthy adult subjects in which a bilateral slight sensorineural hearing loss was detected. A routine hearing test was done as a part of an annual checkup of an entire population of subjects covered by insurance for this purpose. Any other pathologic findings or health complaint was excluded and no known reason for the hearing loss could be found. The control group of 33 subjects with normal audiograms was selected from the same annual checkup group.

The hearing level was significantly different between the groups. The audiogram shape showed a high-tone loss in the majority of the subjects in the experimental group. However, in 5 subjects, a bilateral flat audiogram was evident and in another 2, a slight low-tone loss was seen. It is interesting to note that essentially the hearing loss was found to be symmetrical, but still the mean threshold of the left ear was slightly but consistently higher than that of the right ear (Table 1).

Even though the mean age of each group was 59 years, the combination of slight hearing loss and complaints of reduction in speech discrimination ability (manifested by the results in the discrimination test performed with noise at signal-to-noise ratio of -5 dB) are the difficulties that one faces in subjects with sensorineural hearing loss at an advanced age.

Table 2.—Mean Whole Blood Viscosity in Centipoises*

	Groups				
	Experimental		Control		
Shear Rate, s^{-1}	Mean	SD	Mean	SD	*P*
230	4.91	0.34	4.71	0.34	<.05
115	5.43	0.42	5.17	0.33	<.01
46	6.69	0.55	6.38	0.51	<.05
23	7.75	0.83	7.32	0.75	<.05
11.5	9.97	1.48	9.09	1.09	<.01
5.75	13.18	2.58	11.90	1.94	<.05
2.30	21.21	5.52	19.30	4.65	NS
1.15	32.33	5.73	29.68	5.86	NS

*NS indicates not significant.

Table 3.—Whole Blood Viscosity Results

	Group	
Viscosity Values	Experimental, No. (%)	Control, No. (%)
Normal	18 (54.5)	31 (93.9)
High	15 (45.5)	2 (6.1)

Evaluation of the vestibular system did not reveal significant differences between the two groups. Before conclusions can be drawn on the slight abnormalities found one should remember that the battery of applied tests was limited and perhaps the evaluation of the vestibular function was not sensitive enough.

Many cardiovascular and hematologic factors could affect the adequate blood supply to the ears. This study concentrates on blood viscosity.

The whole blood viscosity average results in the experimental group were higher than in the control group, but the results were still within the normal range, close to the higher border level, and only at two shear rates higher than the normal values. It is assumed that if real high blood hyperviscosity existed, some additional abnormalities as a result thereof or associated with it would exist. Of the total of 66 subjects tested for blood viscosity, in 17 a higher than normal viscosity was evident, and 15 of these 17 belonged to the experimental group.

Thus, the importance of blood viscosity at the starting process of hearing deterioration could be manifested at a relatively early stage, when other complicating factors are not yet evident. A few articles in the literature mentioned a relationship between the rheological features of blood and hearing, and improvement of hearing as a result of improvement in blood flow.[5,8-10]

Browning et al[2] emphasized the abnormal rigidity of the red blood cells as being the cause of sensorineural hearing loss. Experimentally it was demonstrated in guinea pigs that high blood viscosity resulted in diminished oxygenation of the cochlea.[1]

Considering the results of Thomas et al[4] and Willison and Boulay,[11] that even normal hematocrit values, but at the upper limits, could interfere with normal brain circulation, we can assume the vulnerability thereof applies to the cochlea too, as is probably manifested in the experimental subjects. Willison and Boulay[11] indicated that the circulation to the brain could be badly influenced at hematocrit levels of even 0.46. In our experimental group the hematocrit values were a little higher, and this can be assumed to be one of the reasons for the higher blood viscosity. A follow-up study on these groups will possibly elucidate further the features of chronic labyrinthine ischemia.

This study is dedicated to the memory of Moshe Rubinstein, MD.

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Combination Effect of Hyperthermia and Photodynamic Therapy on Carcinoma

Nobuo Matsumoto, MD; Hitoshi Saito, MD; Norio Miyoshi, PhD; Kazuo Nakanishi, MD; Masaru Fukuda, MD

• We investigated the time course of hematoporphyrin oligomer uptake in squamous cell carcinoma transplanted into C3H mice after intraperitoneal injection by measuring its fluorescence intensity. The intensity peaked 83 hours after the injection. The tumors disappeared after an average of 4.12 days with a single application of photodynamic therapy or microwave hyperthermia 83 hours after hematoporphyrin oligomer injection. However, all the tumors treated with these single modalities regrew within 4 weeks after the treatments. Therefore, we investigated the therapeutic effect of microwave hyperthermia in combination with photodynamic therapy. As a result, the combination effect was strongest when high-dose therapy was used as the first choice, irrespective of the order of the treatments, and no tumor regrowth occurred for 45 days.

(*Arch Otolaryngol Head Neck Surg.* 1990;116:824-829)

Recently, photodynamic therapy (PDT) for malignant tumors using hematoporphyrin derivative with an argon dye laser system has been developed. Harris et al[1] reported their initial experience with PDT for human head and neck cancers. However, application of the therapy has been limited to superficial tumors. On the other hand, a sensitizing effect of hematoporphyrin derivative by microwave action has been reported by several authors.[2-5] It has been suggested that a combination of PDT and hyperthermia may be more cytotoxic than the additive effects of the individual modalities in vitro.[6,7] However, there have not yet been any reports concerning this treatment in vivo.

We have already reported that new stable hematoporphyrin oligomers (mean molecular weight, 3000 d) were more effectively incorporated into squamous cell carcinoma (SCC) transplanted into C3H mice than the other hematoporphyrin derivatives.[8]

The purpose of this study, therefore, is to investigate the time course of hematoporphyrin oligomer uptake by malignant tumors, and to find the most effective sequence of combinations of PDT and microwave hyperthermia therapies in vivo using transplanted SCC in C3H mice.

MATERIALS AND METHODS

Malignant Tumors and Administration of Hematoporphyrin Oligomer

C3H/He mice bearing SCC were used in all the experiments. A tumor from a donor mouse was cut into small pieces (about 3 × 3 × 3 mm) and one of these pieces was transplanted subcutaneously into the back of an 8-week-old recipient mouse. The tumor volume was 100 to 200 mm^3 when used for PDT or microwave irradiation.

Hematoporphyrin oligomer (molecular weight, 3000 d; 2.5 mg/mL; Seikagaku-Kogyo Co, Tokyo, Japan) dissolved in physiologic saline solution was intraperitoneally injected (50 μg per gram of body weight).

Fluorescence Measurement

After removing the dermis over the tumors, the tumors were excised from the mice at various times (at 0, 24, 48, 72, 83, 96, and 168 hours) after intraperitoneal injection of hematoporphyrin oligomer. Each tumor was cut into small pieces (2 × 2 × 2 mm^3), plunged immediately into isopentane solution chilled by an acetone-dry ice solution, covered by an embedding compound (Bright CRYO-M-BED, Bright Instrument Co, Huntingdon, England), and chilled to −15°C in a cryostat. Five-micrometer frozen sections were made and the fluorescence intensity of hematoporphyrin oligomer incorporated into the tumor tissue was measured by the reflection method[5] with a fluorescence photometer.

PDT

Photodynamic therapy was carried out for the tumors 2 weeks after transplantation. The light (wavelength, 630±5 nm) from an argon-dye laser (models 171-07 and 375-03, Spectro-Physics Co, Mountain View, Calif) was irradiated on the tumor in a spot 8 mm in diameter with a 3-cm distance from the tip of the fiber at doses of 0 J/cm^2, 17.9 J/cm^2 (50 mW/cm^2), 35.8 J/cm^2

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(100 mW/cm^2), 71.6 J/cm^2 (200 mW/cm^2), and 107.4 J/cm^2 (300 mW/cm^2) 83 hours after intraperitoneal injection (14 mice).

Microwave Hyperthermia

Two weeks after transplantation, microwaves were irradiated on the tumors using a microtizer (2450 MHz; model MT-30, Minato Ikagaku Co, Osaka, Japan) at 43 ± 0.5°C for varying lengths of time (30, 60, and 90 minutes) 83 hours after intraperitoneal injection (15 mice).

Microwave Hyperthermia in Combination With PDT

The following 4 modes of local treatment for the tumors (6 mice in each group) were performed 83 hours after hematoporphyrin oligomer injection. High and low dose were defined as follows: (1) microwave hyperthermia (irradiation time, 60 minutes; high-dose hyperthermia) followed by PDT (a dose of 35.8 J/cm^2; low-dose PDT) within 1 hour; (2) PDT (35.8 J/cm^2) followed by microwave hyperthermia (60 minutes) within 1 hour. (3) microwave hyperthermia (30 minutes; low-dose hyperthermia) followed by PDT (71.6 J/cm^2; high-dose PDT) within 1 hour; and (4) PDT (71.6 J/cm^2) followed by microwave hyperthermia (30 minutes) within 1 hour.

Temperature Measurement

Temperatures in the tumors were monitored during PDT or microwave hyperthermia. The tip of a microthermocouple (Digipanel D 620, Takara Thermister Instruments Co, Yokohama, Japan) was inserted into the center of the tumor base. The tumor temperature did not exceed 39°C in any of the cases during PDT.

Assessment of the Tumor Response

The tumor volume was measured once per day before and after irradiation in order to make a growth curve of the tumor. The macroscopic changes of the tumors treated were recorded by photograph.

Histologic Examination

Tumors were removed from mice immediately before and at varying lengths of time after PDT, hyperthermia, or combined treatments. The removed tumors were fixed in 10% buffered formaldehyde solution, embedded in paraffin, cut in sections (5 μm thick), and stained with hematoxylin-eosin.

Calculation of the Antitumor Effect in Cases of Combination Therapy

In the growth curve, we expressed the antitumor effect as the number of days needed for the tumor to become 75%, 50%, 25%, or 0% of the size at the beginning of irradiation in each series of experiments.

The different antitumor effects among the four treatment groups were statistically analyzed by the Wilcoxon and Mann-Whitney tests (the rank sum tests for two independent samples).[9]

RESULTS

Fluorescence

In frozen sections, the specific red fluorescence of hematoporphyrin oligomer was positive in the fibrous capsule at the periphery of the tumor; in the connective tissue, capillary endothelial cells, and inflammatory cells in the tumor tissue; and especially in the cytoplasmic areas of those cells.

The fluorescence spectra of incorporated hematoporphyrin oligomer were measured by a reflection method. In Fig 1, the relative fluorescence intensity of hematoporphyrin oligomer incorporated into the tumor tissue by intraperitoneal injection was highest at 83 hours after the injection.

PDT

Because it was found that the maximum concentration was at 83 hours after the injection, PDT was carried out for five tumors (five mice) with a dose of 0, 17.9, 35.8, 71.6, or 107.4 J/cm^2 83 hours after intraperitoneal injection on the same day, respectively. In the mouse irradiated with a dose of 17.9 J/cm^2 (Fig 2; curve 1), the growth rate of the tumor was almost the same as that of the control (curve 0) shown in Fig 2. In the mice irradiated with doses of 35.8 and 71.6 J/cm^2 (curves 2 and 3, respectively), the tumors regressed, but did not disappear. On the other hand, in the mouse irradiated with a dose of 107.4 J/cm^2 (curve 4), the tumor disappeared on the eight day after the irradiation, although tumor regrowth occurred on the ninth day after the disappearance.

To evaluate the recurrence, an additional nine tumors (nine mice) were irradiated with a dose of 107.4 J/cm^2. The mean time to disappearance was 4.22 days after the irradiation, but regrowth occurred in all the tumors within 4 weeks after the disappearance. However, no side effects were observed with this highest dose.

Histologic examination disclosed congestion and hemorrhage in the tumor tissue after the irradiation. Although the tumor disappeared macroscopically on the fifth day, the tumor cells remained in deep regions.

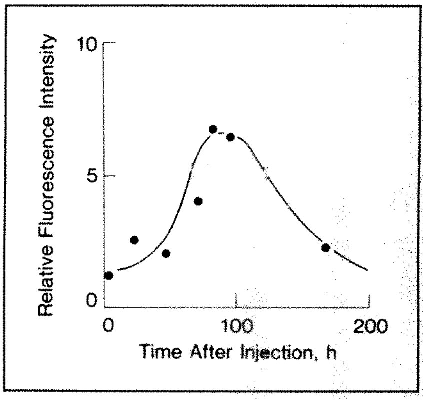

Fig 1.—The fluorescence intensity of hematoporphyrin oligomer in tumors at various times following intraperitoneal injection.

Microwave Hyperthermia

Microwaves were irradiated to three groups (two mice each) at 43 ± 0.5°C, 83 hours after hematoporphyrin oligomer injection for varying lengths of time (30, 60, or 90 minutes) on the same day. In the group irradiated for 30 or 60 minutes (Fig 3; curves 1 and 2), the tumors regressed, but did not disappear, whereas the control (curve 0) grew rapidly, as shown in Fig 3. However, in the group irradiated for 90 minutes (curve 3), two tumors disappeared on the fifth day (mean value) after the irradiation, although tumor regrowth occurred on the 11th day (mean value) after the disappearance.

To determine the recurrent conditions, an additional nine tumors (nine mice) were irradiated for 90 minutes. Those tumors disappeared 4.02 days (mean value) after hyperthermia, but tumor regrowth occurred in all the tumors within 4 weeks after complete response. No side effects were seen with this highest dose.

Histologically, almost the same features as in the PDT cases were observed.

Microwave Hyperthermia in Combination With PDT

Even with a dose of 107.4 J/cm^2 in PDT or with 90 minutes of irradiation in microwave hyperthermia, tumor regrowth took place. Therefore, we attempted to combine microwave hyper-

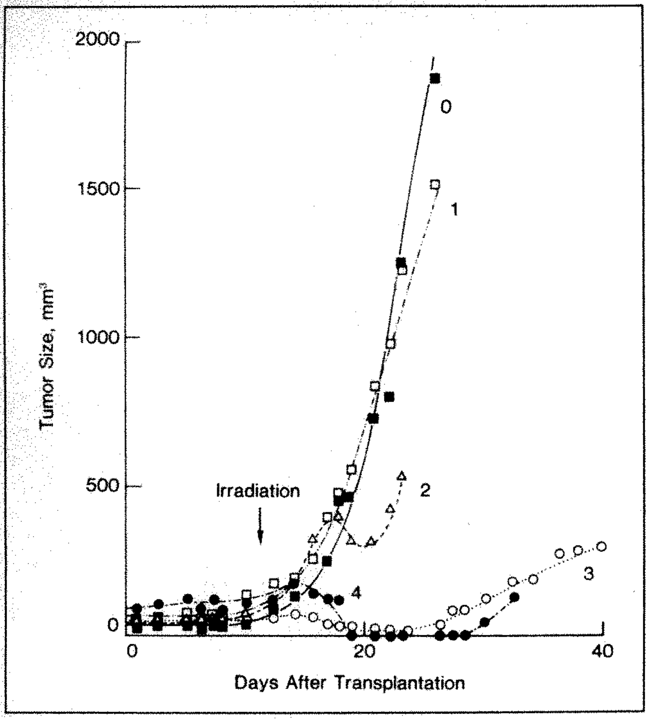

Fig 2.—Dose-response of photodynamic therapy, which was performed on tumors with light (630 ± 5 nm) from an argon-dye laser with doses of 0 (curve 0), 17.9 (curve 1), 35.8 (curve 2), 71.6 (curve 3), and 107.4 (curve 4) J/cm², 83 hours after hematoporphyrin oligomer injection.

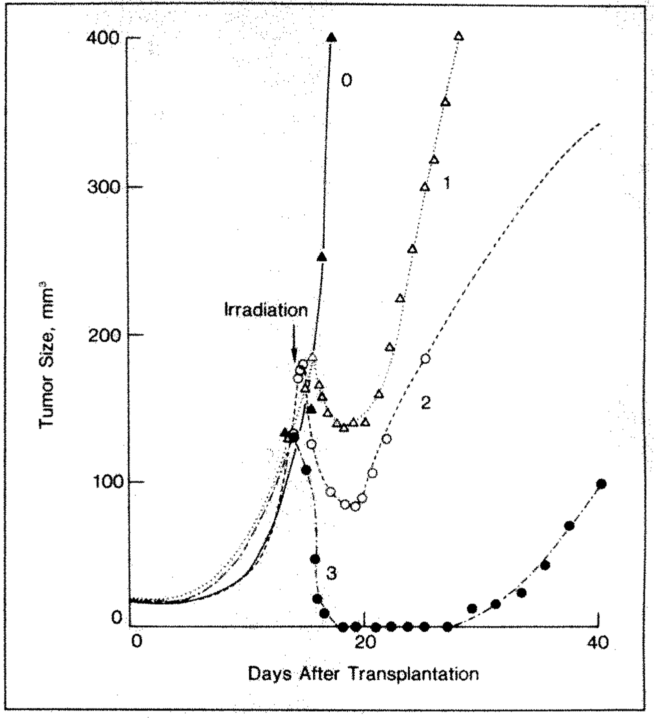

Fig 3.—Dose-response of microwave hyperthermia. Microwaves were irradiated on the tumors using a microtizer (2450 MHz) at 43 ± 0.5 °C for 0 (curve 0), 30 (curve 1), 60 (curve 2), and 90 (curve 3) minutes, 83 hours after hematoporphyrin oligomer injection.

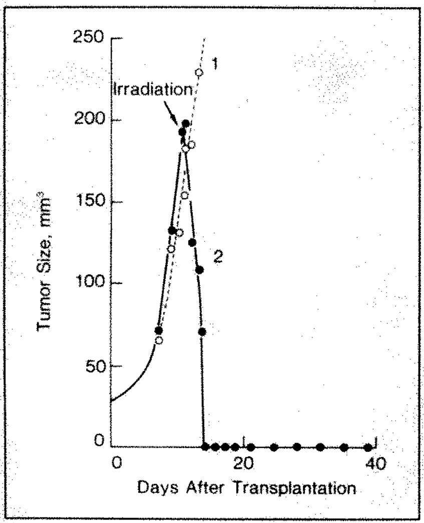

Fig 4.—The growth curve of high-dose microwave hyperthermia followed by low-dose photodynamic therapy. High-dose microwave hyperthermia (3.21 W at 43 ± 0.5 °C for 60 minutes) was immediately followed by low-dose photodynamic therapy (35.8 J/cm²) 83 hours after hematoporphyrin oligomer injection. Curve 1 indicates control tumor; and curve 2, irradiated tumor.

thermia with PDT to accomplish complete tumor abolition.

In the combination of therapies, we used conditions under which tumor disappearance does not occur with each individual therapy (Figs 2 and 3) to investigate the synergistic effects of both kinds of therapies. We used a dose of 71.6 J/cm² in PDT and 60 minutes of irradiation in microwave hyperthermia as the high-dose treatment, and also a dose of 35.8 J/cm² in PDT and 30 minutes of irradiation in microwave hyperthermia as the low-dose therapy. The high-dose form of one kind of therapy was combined with the low-dose form of the other therapy in various sequences as described in the "Materials and Methods" section.

High-Dose Therapy Followed by Low-Dose Therapy.—In the group that received microwave hyperthermia (60 minutes) followed by PDT (35.8 J/cm²), the representative growth curves of irradiated (curve 2) and control (curve 1) tumors are shown in Fig 4. The control tumor grew very rapidly after 10 days. The irradiated tumor regressed very rapidly after the irradiation, and eventually disappeared on the fifth day after irradiation. No tumor regrowth occurred for 45 days after the disappearance of any of the tumors in group 1 or group 4.

Figure 5, top, shows a microscopic view of the tumor before irradiation. Tumor tissue consisted almost entirely of viable tumor cells without any apparent necrotic areas. Just after irradiation, the epidermis still appeared normal, but the tumor was highly congestive and partially hemorrhagic with viable tumor cells. On the first day after irradiation, however, the epidermis was ulcerated, and the tumor tissue was markedly hemorrhagic, mixed with viable and necrotic tumor cells.

Figure 5, bottom, shows a microscopic view of the tumor on the fifth day after irradiation. The lesion was composed of granulated tissue (lower region), covered with inflammatory exudation and neutrophils (upper region), and no tumor cells were found to have remained viable. Even on the 45th day after irradiation, no tumor cells were detectable.

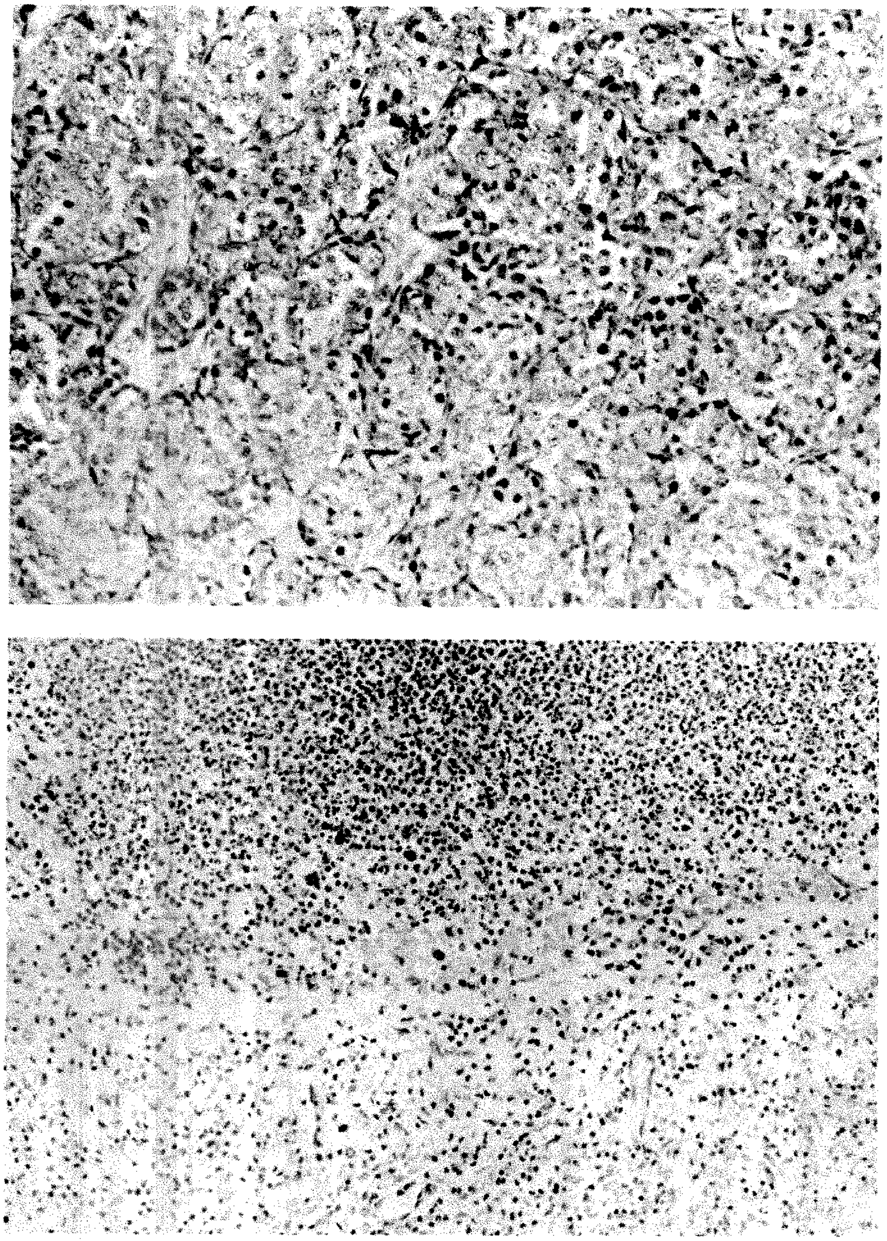

Fig 5.—A microscopic view of the tumor in the case diagrammed in Fig 4. Top, Before irradiation (hematoxylin-eosin, ×50). Bottom, Fifth day after irradiation (hematoxylin-eosin, ×50).

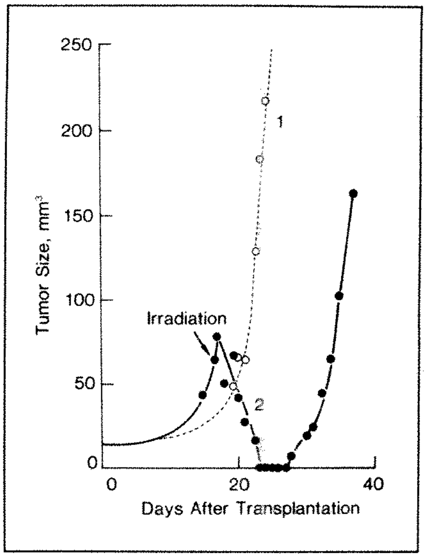

Fig 6.—The growth curve of low-dose photodynamic therapy followed by high-dose microwave hyperthermia. Low-dose photodynamic therapy (35.8 J/cm²) was immediately followed by high-dose microwave hyperthermia (3.54 W at 43 ± 0.5 °C for 60 minutes) 83 hours after hematoporphyrin oligomer injection. Curve 1 indicates control tumor; and curve 2, irradiated tumor.

Low-Dose Therapy Followed by High-Dose Therapy.—Figure 6 shows representative growth curves of irradiated (curve 2) and control (curve 1) tumors. Photodynamic therapy (35.8 J/cm²) followed by microwave hyperthermia (60 minutes) was applied. The irradiated tumor disappeared on the seventh day after irradiation, but tumor regrowth occurred 12 days after that. Tumor regrowth occurred within 4 weeks after the tumor disappearance in all tumors in groups 2 and 3.

A macroscopic view of these tumors is shown in Fig 7. A round subcutaneous tumor (left) disappeared on the seventh day after irradiation (center), but tumor regrowth occurred on the 12th day after irradiation (right).

Assessment and Data Analysis of Tumor Response.—In the growth curves (Figs 4 and 6), the antitumor effect is shown as the number of days needed for the tumor to become 75%, 50%, 25%, or 0% of its initial size. We calculated the values for all the tumors in each series of experiments. In the Table, it is shown that the groups of tumors treated with high-dose therapy as the first choice, irrespective of microwave hyperthermia or PDT, were reduced very rapidly.

The significance of these differences among the four treatment groups was analyzed using the Wilcoxon and Mann-Whitney tests (rank sum tests). The antitumor effects that decreased tumor size to 75%, 50%, 25%, or 0% were significantly greater in groups 1 and 4 than in groups 2 and 3 at the $P=.01$ significance level.

COMMENT

In spite of the generalization that hematoporphyrin derivative accumulates in malignant tissue to a higher degree than in normal tissue, the modalities and mechanisms are still unknown in detail. Gomer and Dougherty[10] reported that the amounts of carbon 14 or tritiated hematoporphyrin derivative that localized in the transplanted tumor tissue of mice at various times following intraperitoneal injection were greater than those in the skin or muscle, but were less

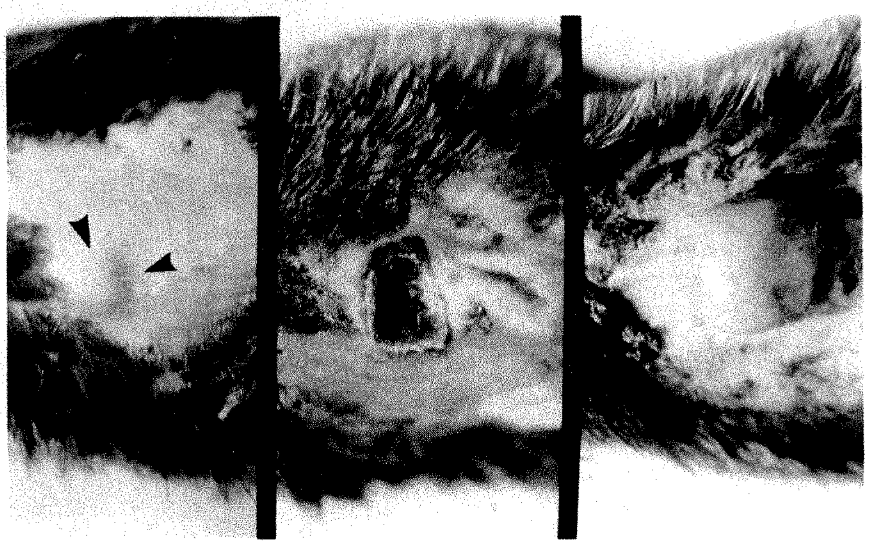

Fig 7.—Macroscopic changes in the case of Fig 6. Before (left; arrowheads), 7 days after (center), and 12 days after (right) irradiation.

A Comparison of the Antitumor Effects of the Combination Therapies[*]

	Mean Times of Tumor Decrease, d			
Tumor Size[†]	Group 1	Group 2	Group 3	Group 4
75%	0.87	4.69	4.48	0.17
50%	1.33	6.21	7.09	0.67
25%	1.68	8.00	8.00	1.53
0%	2.15	9.71	8.77	2.91

[*] Group 1 subjects received microwave treatment for 60 minutes followed by laser treatment (35.8 J/cm^2); group 2, laser treatment (35.8 J/cm^2) followed by microwave treatment for 60 minutes; group 3, microwave treatment for 30 minutes followed by laser treatment (71.6 J/cm^2); and group 4, laser treatment (71.6 J/cm^2) followed by microwave treatment for 30 minutes.

[†] Expressed as percent of original size.

than those in the liver, kidney, or spleen.

Gomer and Dougherty[10] also reported that the maximum carbon 14 and tritiated hematoporphyrin derivative levels in all the tissues of mice including tumors were usually obtained after 3 to 4 hours, and that this was followed by a plateau in accumulation for the next 44 or 45 hours following injection.

On the contrary, we found that the relative fluorescence intensity of hematoporphyrin oligomer incorporated into the tumor was strongest at 83 hours after injection.

The difference between our results and those of Gomer and Dougherty may be attributable to the different molecular sizes of the photosensitizer used. Namely, the molecular weight of hematoporphyrin oligomer (3000 d) used in our experiments is over three times as large as that of Photofrin I (below 1000 d), used by Gomer and Dougherty. It is possible that hematoporphyrin oligomer with a larger molecular size needs more time for incorporation, accumulation in the tumor tissue, and removal from the tissue than Photofrin I.

Before application of the combined therapy, we investigated the therapeutic effect of a single treatment of PDT and microwave hyperthermia. As a result, although the tumors initially disappeared, all the irradiated tumors regrew within 4 weeks after these treatments.

In the combination therapies, the effect was strongest and no tumor regrowth occurred for 45 days when high-dose therapy was used as the first choice of therapy, irrespective of PDT or microwave hyperthermia.

The combination effect of PDT and microwave hyperthermia on transplanted carcinoma has been reported by Waldow et al[11] and Henderson et al.[12] According to their reports, the combination effect was strongest when PDT was used as the first choice of therapy. In their experiments, the dose of PDT was 135 J/cm^2 and the irradiation time of microwave hyperthermia was 30 minutes. Photodynamic therapy with a dose of 135 J/cm^2 was considered high-dose therapy in our experiment, and microwave hyperthermia for 30 minutes was considered low-dose therapy. Therefore, our results coincide with theirs.

No dominant side effects have been reported in animal experiments with the high-dose conditions mentioned above.

The reason why the antitumor effect was strongest when high-dose therapy was used as the first choice may be among the following:

1. There may be a tolerance phenomenon in tumor cells to hyperthermic or photodynamic action. The existence of thermotolerance has been repeatedly reported.[13-17] Recently, it was reported that step-down heating, ie, high-dose hyperthermia followed by low-dose hyperthermia, reduced thermotolerance,[18-20] but there was large thermotolerance in the case of step-up heating, ie, low-dose hyperthermia followed by high-dose hyperthermia.[18,21] The good effects obtained by the sequence of high-dose therapy followed by low-dose therapy used in our experiment resemble those seen in step-down heating, although the mechanism of photodynamic action may be different from that of hyperthermic action.
2. Tumor cells may be capable of repairing DNA damage. In the case of low-dose therapy followed by high-dose therapy, the insufficient effect of the first therapy may induce repair.
3. A part of the hematoporphyrin oligomer molecule may be inactivated by the low-dose PDT preceding high-dose microwave hyperthermia.

The molecular mechanism of the effectiveness of PDT is attributable to the cytotoxic effect of singlet oxygen produced by hematoporphyrin derivative irradiated with visible light.[22,23] On the other hand, Nakajima et al,[2] Tatsuta et al,[3] and Miyoshi et al[5] reported that superoxide radical anions were generated when tumor cells containing hematoporphyrin derivative were irradiated by microwaves. The target of the active oxygen species is thought to be the blood vessels observed as congestion and hemorrhage in the tumor tissue.

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T2 Glottic Cancer

Recurrence, Salvage, and Survival After Definitive Radiotherapy

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• The records of all patients with T2, N0 squamous cell carcinoma of the true vocal cords treated with definitive radiotherapy at The University of Texas M. D. Anderson Cancer Center between 1970 and 1985 were analyzed to investigate treatment outcome, prognostic factors associated with tumor recurrence, and the potential impact of improved initial treatment on patient survival. There were 114 patients (male to female ratio, 13:1) with a median age of 62 years at presentation. All were treated with external beam irradiation to a modal dose of 70 Gy in 35 fractions over 7 weeks. The median field size was 25 cm^2 and no elective treatment to the neck was routinely given. The crude recurrence rate after definitive radiotherapy was 32%. Of the 37 local regional failures, 32 were in the larynx only, 3 in the neck, and 2 in both the larynx and the neck. All patients who had recurrence after radiotherapy underwent salvage procedures, which increased the ultimate control rate above the clavicles to 94%. Overall and disease-specific survival rates at 5 years were 69% and 92%, respectively. Fifty patients died: 7 of laryngeal cancer, 2 of complications of salvage surgery, 13 of unrelated second cancers, and 28 of other intercurrent disease. The prospects for improved survival through more effective initial treatment of this stage of glottic cancer are therefore very limited. Significant complications of radiotherapy occurred in only 4 patients (3.5%), and overall, 74% of patients retained a functional larynx. Analysis of a wide variety of patient-, tumor-, and treatment-related variables failed to identify any statistically significant prognostic factors. In the absence of reliable predictors of treatment failure, we continue to recommend definitive radiotherapy for patients with T2, N0 glottic cancer. Since isolated neck recurrences are rare (2.6%), elective neck irradiation is not recommended. However, in patients undergoing salvage surgery for recurrence, postoperative radiotherapy to the stoma, neck, or both is advocated when the surgical pathologic examination reveals recurrent disease in the subglottis or thyroid cartilage, or extranodal disease in the neck. The treatment plan used in these circumstances is described.

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Optimal treatment of laryngeal cancer demands both tumor eradication and preservation of laryngeal function. Radiotherapy achieves this result in over 90% of patients with T1 glottic cancers, but tumor control declines progressively with increasing T stage. Although some radiation failures can be salvaged by conservation surgery, a total laryngectomy is usually required. Methods to improve tumor control without sacrifice of the larynx include conservative surgical procedures, use of modified radiation dose fractionation schedules, and use of induction chemotherapy prior to definitive irradiation. It has been a traditional policy of this institution to treat most T2 glottic cancers by definitive radiotherapy. Rational application of possible alternative therapies requires analysis of causes and patterns of failure with conventional radiation therapy alone. This study was undertaken to (1) review the results of treatment of T2, N0 glottic cancers by radiotherapy alone at The University of Texas M. D. Anderson Cancer Center, Houston, with particular reference to the patient-, tumor-, and treatment-related parameters associated with tumor recurrence, and (2) examine the potential impact of improved local disease control on patient survival.

MATERIALS AND METHODS

Patient Population

Between January 1970 and December 1985, 114 patients with previously untreated, biopsy-proved T2, N0 squamous cell carcinoma of the glottis were treated with definitive radiotherapy at M. D. Anderson Cancer Center. The patient population con-

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sisted of 101 men and 13 women with a median age of 62 years (range, 38 to 76 years). The majority (82%) were identified as cigarette smokers, with a median exposure of 40 pack-years; 15% had an uncertain smoking history; and only 3% were identified as nonsmokers. Performance status was not formally recorded in the majority of cases. However, most patients were in good to fair general condition.

All the patients were staged clinically and radiologically. Most patients were referred after endoscopy and biopsy had been performed. Direct endoscopic evaluation was limited to those patients who presented without a histologic diagnosis or for whom direct laryngoscopy was considered essential for accurate delineation of disease. Radiologic examinations included conventional tomography, laryngography, and computed tomography, the latter being introduced for routine staging in 1982. All patients were evaluated by both a surgeon and a radiotherapist.

The American Joint Committee on Cancer criteria[1] for stage T2 are (1) extension of disease from the vocal cords to the supraglottis or subglottis, (2) impaired movement of the vocal cord without fixation, or (3) both. The distribution of patients by criteria for T2 staging is shown in Fig 1.

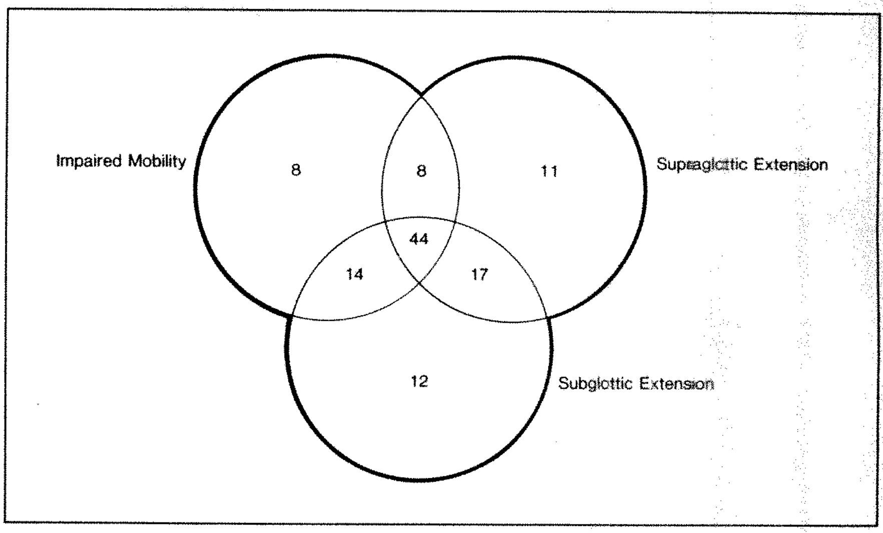

Fig 1.—Distribution of patients with T2 glottic carcinoma according to staging criteria.

Treatment

All patients received definitive external beam irradiation (111 received cobalt 60 γ rays, and 3 received 6 MV x-rays) to total doses of 65 to 78 Gy in 6 to 8 weeks. The modal dose was 70 Gy in 35 fractions, and 88 patients (77%) received 70 ± 2.5 Gy. Ten patients in this series were treated with hyperfractionated irradiation to doses ranging from 74.4 to 76.8 Gy at 1.2 Gy per fraction twice daily. Forty-three patients were treated with ipsilateral fields only; the remainder were treated with parallel opposed bilateral fields. The median field size was 25 cm^2 (range, 16 to 100 cm^2). Dosage was specified at the mid-vocal cord. Wedges were used only when disease was present in the posterior half of the vocal cord.

All 37 patients whose primary radiotherapy failed underwent surgical salvage consisting of total laryngectomy in 30 patients (2 with simultaneous neck dissection), 1 hemilaryngectomy only, 3 neck dissections only, and 3 endoscopic laser ablations. Nine of the 37 patients whose initial treatment failed received additional radiotherapy for further recurrence after attempted surgical salvage.

Follow-Up and End Points of Study

Follow-up information was obtained from clinic visits to M. D. Anderson Cancer Center, or by letters from referring physicians. All but 3 living patients were followed up from 36 to 192 months. Fifteen patients died without evidence of recurrence above the clavicles before 36 months of follow-up.

The primary end points of the study were to determine the probability of control of T2 glottic cancers by radiotherapy alone and after surgical salvage, to examine patient-, tumor-, and treatment-related parameters associated with an unsuccessful outcome, and to analyze survival and causes of death in this patient population, with particular reference to subsequent primary cancers outside the larynx. Criteria for distinguishing between lung metastases from the index laryngeal cancer and second primary lung cancers were (1) time greater than 5 years to development of lung lesion, and/or (2) different histopathologic features.

Life-table analyses were performed using the method of Berkson and Gage.[2]

RESULTS

Local and Regional Disease Control

Of the 114 patients treated with definitive radiotherapy, local and/or regional failure occurred in 37: 32 (86%) in the larynx, 2 in both the larynx and neck, and 3 in the neck only. Of the recurrences, 25 (68%) occurred within the first 2 years, 7 (19%) between 25 and 60 months, and 5 (14%) from 61 months to 15 years after treatment. Although late recurrences may have been second laryngeal primary cancers, they were scored for this analysis as treatment failures.

Surgical salvage was attempted in all 37 patients whose primary therapy failed; 30 of these patients received total laryngectomy. The outcome of treatment of first recurrences by site of recurrence and treatment technique is shown in Table 1. Local-regional disease control was achieved in 28 patients (76%). Of the 9 second recurrences, further treatment secured local-regional control in 5 (Table 2). Ultimate local control through the time of death or last follow-up was therefore obtained in all but 4 patients, and 84 patients (74%) retained a functional larynx.

Distant Metastases

No patient whose primary cancer was controlled had a relapse at a distant metastatic site. However, of the 37 patients who underwent salvage for local recurrence, regional recurrence, or both, 7 later developed distant metastases. Four of these (3 with lung metastases and 1 with skin metastases to the scalp) survived 30 to 94 months after salvage surgery for metastatic disease and died of other causes.

Survival

Fifty of the 114 patients died. A breakdown of causes of death is shown in Table 3. Absolute and disease-specific survival is shown in Fig 2. Most patients died of causes unrelated to their index laryngeal cancer.

Second Cancers

The cumulative probability of developing a second cancer (other than skin

Table 1.—Outcome of Treatment of First Recurrences (37 Patients)*

Site of Recurrence	Laryngectomy Only	Laryngectomy and Neck Dissection	Neck Dissection	Neck Dissection and Radiotherapy	Hemilaryngectomy	Laser
	Local-Regional Control by Treatment Modality					
Larynx	23/28	...	...	...	1/1	1/3†
Neck	...	...	1/1	2/2	...	...
Larynx and neck	...	0/2	...	...	...	...

* Entries indicate number of patients whose first recurrence was controlled over the number of patients treated.

†Although disease recurred in two patients treated by laser therapy, both recurrences were controlled by subsequent laser ablations.

Table 2.—Outcome of Treatment of Second Recurrences (9 Patients)*

Site of Recurrence	Surgery and Radiation Therapy	None	Laser
	Local-Regional Control by Treatment Modality		
Stoma	2/3	0/1	...
Neck	1/3	...	...
Larynx	...	...	2/2

* Entries indicate number of patients whose second recurrence was controlled over the number of patients treated.

Table 3.—Causes of Death

	No. of Patients
Index cancer	
Recurrence above clavicles	4
Distant metastases	3
Surgical complications	2
Second cancers	13
Other intercurrent disease	28
Total	**50**

cancer) after diagnosis of the glottic cancer is depicted in Fig 3. At 10 years, the risk was 27%. The distribution of second cancers is shown in Table 4. Second cancers most frequently occurred in the lung and esophagus. The actuarial probability of death due to lung or esophageal cancer was 18.7% at 10 years, compared with 11.7% for the index glottic cancer. Two patients had second primary cancers, synchronous with their laryngeal cancer: one adenocarcinoma of esophagus and one small-cell lung cancer. Two additional patients (not included in the actuarial probability estimate of second primaries) had glottic cancer as their second and third primary cancers.

Factors Influencing Outcome of Primary Radiotherapy

Patient-Related Variables.—No correlation was observed between the outcome of radiotherapy and age, sex, or amount of tobacco use. Treatment failed in 19 (35%) of 55 patients below the median age of 62 years, compared with 18 (31%) of 59 patients 62 years or older. Treatment failed in 5 (39%) of 13 women and in 32 (32%) of 101 men. Cigarette consumption was quantitated in 84 patients. Of 31 patients with a median history of 40 pack-years or less, treatment failed in 11 (35%). Of the 53 patients with a smoking history of greater than 40-pack years, treatment failed in 15 (28%).

Tumor - Related Variables. — *Histology.*—All patients had squamous cell carcinomas. Histologic grade was specified in only 67 patients, of whom 12 had well-differentiated, 47 moderately differentiated, and 8 poorly differentiated tumors. Because of the incomplete data, no definite conclusions can be drawn regarding the probability of treatment failure by tumor grade. However, the observed recurrence rates for well-, moderately, and poorly differentiated tumors (3 of 12, 10 of 47, and 3 of 8, respectively) do not suggest any systematic relationship.

Sites of Extension.—Pairwise comparisons for the probability of recurrence vs sites of tumor extension were tested separately for the anterior commissure, contralateral true cord, ventricles, false cords, arytenoids, aryepiglottic folds, infrahyoid epiglottis, and subglottis. Of these, only subglottic extension, as a single variable, was associated with treatment failure. Subglottic extension was recorded in 87 patients, of whom 33 (38%) suffered local recurrence compared with 4 (15%) of 27 without initial subglottic extension. The significance of subglottic extension as a prognostic factor disappeared, however, in multivariate analysis. Furthermore, review of the failures among the 33 cases with initial subglottic extension who underwent salvage laryngectomy showed that only 7 patients had pathologic evidence of recurrence in the subglottis. The extent of initial subglottic extension measured radiographically in these patients varied from 0.4 to 2.6 cm.

Cord Mobility.—Impaired cord mobility was not associated with treatment failure: only 20 (27%) of 73 with impaired mobility recurred, compared with 17 (41%) of 41 without demonstrated cord mobility.

Criteria for T2 Staging.—The number and combinations of criteria for T2 staging were also tested for prognostic significance (Fig 4). No combination of factors was significant by multivariate analysis.

Treatment-Related Variables.—*Total Dose.*—Total doses varied from 65 to 78 Gy. However, 88 of the 114 patients received tumor doses of 70 ± 2.5 Gy. This uniformity of dose prescription precluded any meaningful dose-response analysis.

Treatment Technique.—There was no correlation between treatment outcome and size of radiation therapy fields. There were 19 (36%) of 53 failures with fields ≤25 cm², compared with 18 (29.5%) of 61 in patients with larger field sizes. The influence of field size was tested separately in the 87 patients who presented with initial subglottic extension. Again, no field size dependence could be demonstrated.

The field orientation also did not influence outcome regarding tumor control: 12 (28%) of 43 patients treated with ipsilateral fields suffered a local recurrence, compared with 25 (35%) of 71 treated with parallel opposed fields.

Fractionation.—All but 10 patients received conventional fractionation: 1 treatment per day and 5 treatments per week. The remaining 10 patients were treated with a hyperfractionated regimen consisting of 1.2 Gy twice daily, 5 days per week. Of the latter, only 2 relapsed. However, these patients had less follow-up than the remainder of the series, and the sample

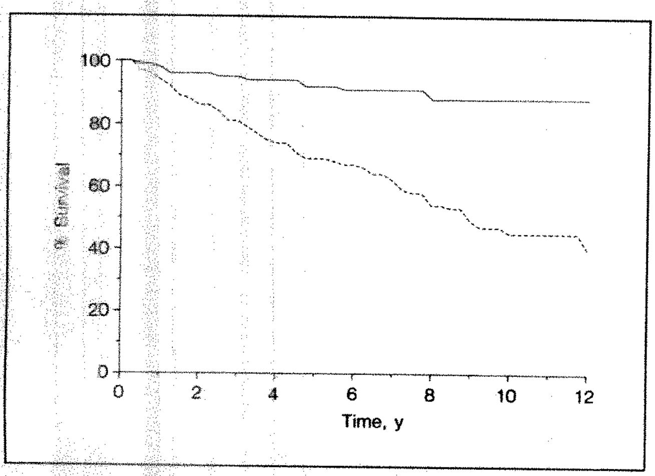

Fig 2.—Absolute and disease-specific survival. Solid line indicates glottic cancer, and dotted line, all causes.

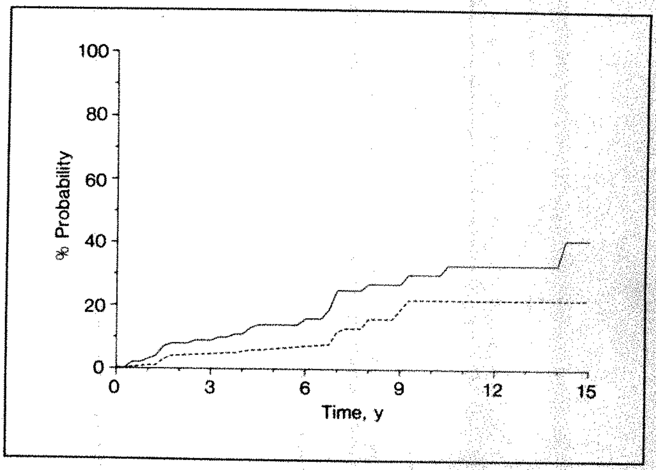

Fig 3.—The cumulative probabilities of developing a second cancer and of death due to a second cancer. Solid line indicates incidence, and dotted line, cause of death.

size is insufficient to provide a valid comparison of treatment efficacy.

Treatment Years.—There was a modest (statistically insignificant) trend toward improved results in more recent treatment years. Five-year local recurrence rates were 34% for patients treated before 1975, 23% for those treated between 1975 and 1980, and 27% for those treated since 1980.

Complications of Treatment.—There were five moderate to severe treatment complications in the entire series. Three other patients had mild arytenoid edema, which resolved spontaneously within 12 months. On an actuarial basis, this translates into a cumulative probability of a significant complication rate of 4.6% at 5 years. The nature of the complications and their treatments are shown in Table 5. The influence of various treatment factors on the risk of complications was examined. There was no significant influence of field size. However, 3 of the 4 patients with moderate to severe complications were treated with unilateral fields only (P=.056).

Table 4.—Incidence of Second Primaries*

Time to Second Primary Tumor, mo	Site, No. of Cases					
	Lung	Esophagus	Head and Neck	Lower GI/ Hepatic Biliary	Other	Total
0-24	2	2	0	1	3	8
25-60	1	1	1	2	0	5
>60	7	1	0	1	1	10
Total	**10**	**4**	**1**	**4**	**4**	**23**

*GI indicates gastrointestinal.

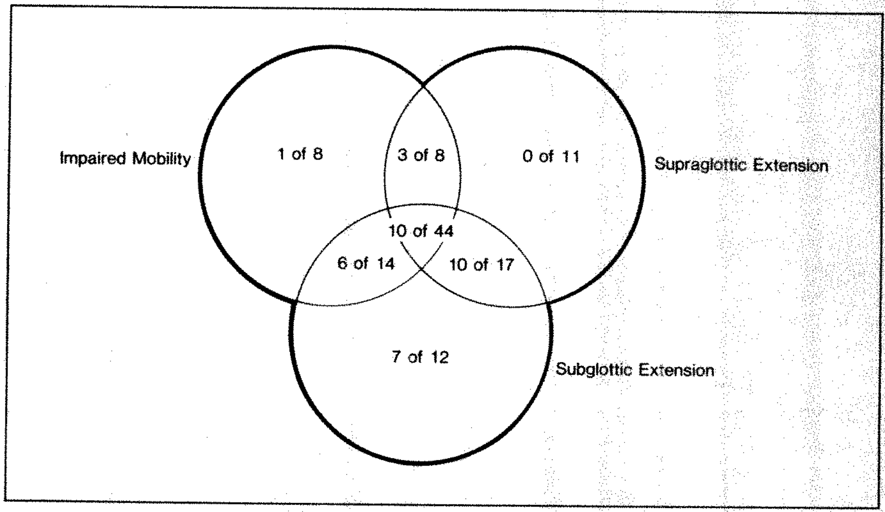

Fig 4.—Local-regional failure by extension of disease.

COMMENT

We undertook this review in an effort to identify factors that might improve the rates of larynx preservation, disease control and survival in patients with T2 N0, M0 glottic cancer. Most reported series of T2 glottic cancers treated by definitive radiotherapy show local control rates in the range of 65% to 75%.[illegible] Surgical salvage of patients whose radiation treatment failed was accomplished in the majority of patients but was seldom compatible with larynx preservation. Certain T2 lesions can be treated primarily by hemilaryngectomy.[13] However, voice quality following hemilaryngectomy is significantly inferior to that achieved by successful radiation therapy. It is, therefore, desirable to identify patients at high risk of radiation therapy failure so that they could be considered for hemilaryngectomy, while others would not be denied radiation therapy

Table 5.—Complications of Treatment

Complication	Treatment	Time to Resolution, mo
Severe arytenoid edema	Temporary tracheostomy	13
Laryngeal stenosis	Temporary tracheostomy	6
Anterior laryngeal web	Laser ablation	13
Soft-tissue necrosis*	Temporary tracheostomy	14
Cartilage necrosis*	Hyperbaric oxygen	14

*Occurred in the same patient.

Table 6.—Review of Previously Published Series of T2 Glottic Carcinoma

Source, y	No. of Patients	Local Control, % (5 y)	Ultimate Control, % (5 y)	Claimed Prognostic Factors
Mendenhall et al,[10] 1988	108	77 T2a, 72 T2b	...	Tumor volume as judged by type of alternative surgery
Karim et al,[9] 1987	156	78	92	Cord mobility
Wang,[18] 1986	190	71 actuarial, 79 T2a, 61 T2b	85	Cord mobility; sex
Amornmarn et al,[14] 1985	34	88	94	Tumor volume; subglottic extension
Van den Bogaert et al,[11] 1983	61	62 T2a, 65 T2b	81 T2a, 78 T2b	Cord mobility and subglottic extension
Chacko et al,[15] 1983	25	66, 78 T2a, 46, T2b	...	Cord mobility; sex
Harwood et al,[7] 1981	244	69 overall actuarial, 80 T2a 52 T2b	84 actuarial	Cord mobility; field size (for T2a)
Woodhouse et al,[19] 1981	42	52	...	Tumor dose
Fletcher,[3] 1980	175	73.7 absolute	94 absolute	Cord mobility; subglottic extension
Kun and van Andel,[16] 1978	43	58 T2b (3-y determinate recurrence-free rate)	...	...
Quayum et al,[17] 1978	24	70 5-y disease free (corrected for death from other causes)	...	Cord mobility; sex

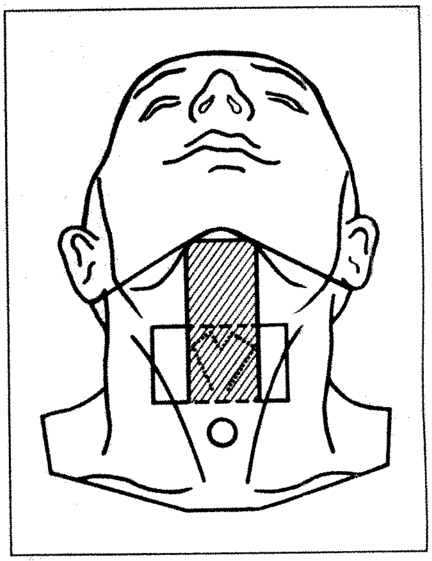

Fig 5.—Treatment fields for elective irradiation after salvage surgery.

for cancers that are likely to be controlled. Numerous authors have claimed that various clinical criteria have prognostic significance (Table 6).[3,7,9-11,14-19] In our analysis, none of these factors was individually significant. The discrepancy in prognostic features between different series is largely attributable to the rarity of the disease, especially among females. For example, 101 male and 13 female patients entered this study over a 16-year period, during which more than 4 000 patients with head and neck cancer were irradiated. Other parameters such as field size dependence or lack thereof most likely reflect differences in treatment practice and setup in different institutions. Also contributing to the discrepancy in reported prognostic factors in different series is the variability of diagnostic methods used, both among institutions and over time within the same institution. We conclude that no clinical prognostic factor is sufficiently robust to permit selection of patients for primary surgical therapy. Whether newer biologically based predictive assays, such as measurement of intrinsic cellular radiosensitivity, will permit this discrimination in the future remains unanswered.[20] In the meantime, we believe that primary definitive radiotherapy is indicated for all T2 patients, and we are presently investigating hyperfractionated radiotherapy as an alternative to conventional fractionation.[21-23]

All reported series have been characterized by a predominance of "in-field" treatment failures. In our study, 34 (92%) of 37 recurrences had a component of in-field failure. Only 3 patients (2.6%) whose primary tumor had been controlled had recurrent disease in the neck alone. Use of large fields to cover potential lymph node metastases cannot be recommended as routine practice. Surgical salvage in our series was associated with subsequent recurrence in 14 (38%) of 37 patients; in 9 of these, disease recurred above the clavicles. Elective postoperative irradiation after salvage laryngectomy is not usually considered because of the risks of retreatment and possible radiation sequelae. We believe, however, that certain pathologic features after surgical salvage, such as subglottic extension, thyroid cartilage invasion, and extranodal disease in the neck, carry a risk of stomal recurrence, neck recurrence, or both sufficient to justify elective postoperative irradiation. The plan we currently use for such situations is indicated in Fig 5. Patients are positioned supine with the head in hyperextension and treated with anterior and posterior cobalt 60 fields. A custom midline block is cut to shield the pharynx down to the level of the lower border of the original lateral fields. With this field arrangement, retreatment is limited to a triangle of tissue on either side of the anterior aspect of the neck. Using dose weightings of 3:2 (anterior to posterior), a dose of 50 Gy at 2 Gy per fraction is administered to the midneck bilaterally. A posterior cord block is used to keep the dose to the spinal cord in the lower neck to 45 Gy. Areas of pathologically determined high risk are boosted with electrons of appropriate energy to a maximum of 60 Gy.

T2 glottic cancer itself usually is not the cause of death. In our series of 114 patients, only 7 died of their index cancer, while another 2 died of perioperative cardiovascular complications associated with salvage surgery. The risk of death from second, unrelated cancers exceeded that from glottic cancer. Second cancers were identified in 23 patients and were the cause of death in 13. Many authors[24-30] have noted an increased risk of cancers of the lung, esophagus, and other head and neck sites in patients cured of early glottic cancer. In a study of 740 patients, Wagenfield et al[30] reported a cumulative risk of a second respiratory tract cancer of 12% at 10 years, with an observed-to-expected ratio of 4:1. In our series, the cumulative risk of second primary tumors in the lung or esophagus was 22% at 10 years. Because of this high risk and the lethal nature of these second primary tumors, patients with cured, early-staged laryngeal cancer should be considered for protocols to evaluate prospective endoscopic screening[31] or the use of chemical inhibitors of cancer promotion, such as the retinoids.

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The Pressure Exerted by Mucoceles in the Frontal Sinus

An Experimental Study in the Cat

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• The pathophysiologic process that results in bone erosion from frontal sinus mucoceles has long been a mystery. Traditionally, bone erosion has been attributed to pressure. However, no scientific evidence has yet been presented to support this hypothesis. To answer this question, seven cats had a mucocele created in one frontal sinus, with the other sinus left as a control. A manometer was inserted into each frontal sinus. Pressure readings were taken over a 7-month period. Pressures on the mucocele side were higher than on the control side and were sufficient to erode bone. Bone was thicker on the mucocele side than on the control side. This study established that mucoceles exert sufficient pressure to erode bone, and that such erosion may be part of a two-stage process.

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The occurrence of cystic lesions within the paranasal sinuses has only been recognized since the early 1800s.[1] Not surprisingly, there is evidence of their appearance much earlier. Canalis[2] described a skull from the Third Century AD that had changes consistent with a chronic cystic lesion of the frontal sinus. In 1524, King Francis I of France recovered from a grave illness that was consistent with an infected frontal sinus cyst.[3] Originally called *hydatid cysts*, these lesions have been known as *mucoceles* since Rollet coined the term in 1896.[4]

For many years there has been uncertainty over the exact definition of a mucocele.[5-7] The uncertainty arises from the lack of experimental investigation of sinus disease, the multiple causes of mucoceles, and the ever-changing philosophies of treatment.[6-8] The best definition seems to be that of Canalis[5]: "chronic, expansile cyst-like lesion(s) of the paranasal sinuses . . . (which) contain sterile, mucoid secretions and are limited by the mucosa of the affected cavity." This definition captures the essence of the lesion, regardless of whether it was caused by chronic infection, trauma, or intrinsic mucosal factors such as cystic fibrosis.

Erosion of the bony sinus walls has frequently been noted in association with mucoceles, must notably in the frontal sinus. Various mechanisms have been proposed to explain this erosion, but most authors currently regard pressure effects as the most likely.[9-13] However, the amount of pressure exerted by a mucocele, if any, has never been measured. This study was designed to measure the pressure exerted by a mucocele where it abuts the sinus wall, and to document the histologic changes at that point.

MATERIALS AND METHODS

Seven preconditioned cats were premedicated with ketamine hydrochloride (20 mg/kg) and acepromazine (1.0 mg/kg). Halothane was administered during the procedure via endotracheal tube to maintain anesthesia.

Using sterile technique, a brow incision was made and a myocutaneous flap was reflected posteriorly. The pericranium was incised and elevated off the skull in a small area overlying each frontal sinus. A single 6-mm burr hole was made through the anterior wall of each frontal sinus. Through this burr hole, the mucosa of the experimental sinus was vigorously curetted using a small right-angled hook. The fronto-nasal duct was plugged with a bloc of temporalis muscle. The control sinus was not manipulated after the burr hole was made. The control and experimental sides were alternated with each successive cut.

Into each burr hole, a manometer (Fig 1)

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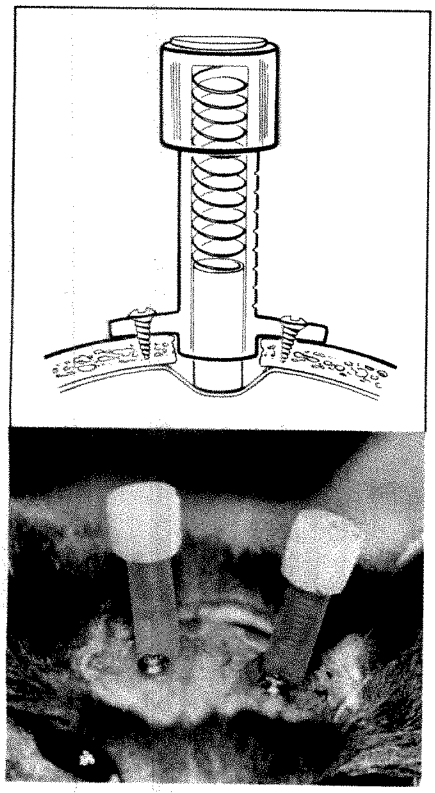

Fig 1.—Top, Schematic drawing of manometer showing spring-loaded piston-in-cylinder construction. Bottom, Photograph showing manometers in place in the cat.

was placed and fixed with two surgical steel screws. The myocutaneous flap was replaced into its anatomic position, slits having been made in it to accept the protruding manometers. The wound was closed with absorbable sutures. All cats were given one preoperative and two postoperative 60-mg doses of cefazolin sodium.

A specially designed manometer was used (Fig 1). It consisted of a spring-mounted acrylic piston that protruded 3 to 4 mm into the sinus. The piston was housed in a transparent dimethicone (Silastic) cylinder screwed to the outside of the cat's skull. The piston could be observed within this cylinder and its displacement measured directly on a millimeter scale etched on the surface of the cylinder.

The amount of displacement is proportional to the pressure exerted on the piston from within the sinus. The exact relationship of pressure to displacement was determined for each manometer by placing it on a Mettler balance and displacing the piston for distances of 1, 2, and 3 mm with a micromanipulator. In this way, a "spring constant" was derived for each manometer and used to calculate the amount of pressure applied to the piston for any given displacement. This was done for each manometer prior to its implantation and after its removal from the sinus. Any difference between these two measures was assumed to result from linear drift, and pressure readings were adjusted accordingly.

MATHEMATIC CONVERSION

The displacement of the manometer's piston was converted into a pressure reading (in millimeters of mercury) by the use of the following logic. First, the amount of mass required to displace the piston was determined for each manometer for each of three predetermined distances (1, 2, and 3 mm) using a Mettler balance and a micromanipulator. This measurement (k) was converted to a spring constant of force (K) in units of dynes per centimeter using the following formula:

$$K = k \times g \times 10$$

where $g = 9.8 \times 10^2$ cm/s^2 (acceleration of gravity), and the factor "10" is used to convert from millimeters to centimeters.

In the experimental situation,

$$F = K \times d$$

where F is the force applied to the piston by the mucocele, and d is the measured displacement of the piston. Then,

$$P = F/A$$

where P is the pressure and A the area of the piston face contacting the mucocele. Substitution yields the following:

$$P = (K \times d)/A$$

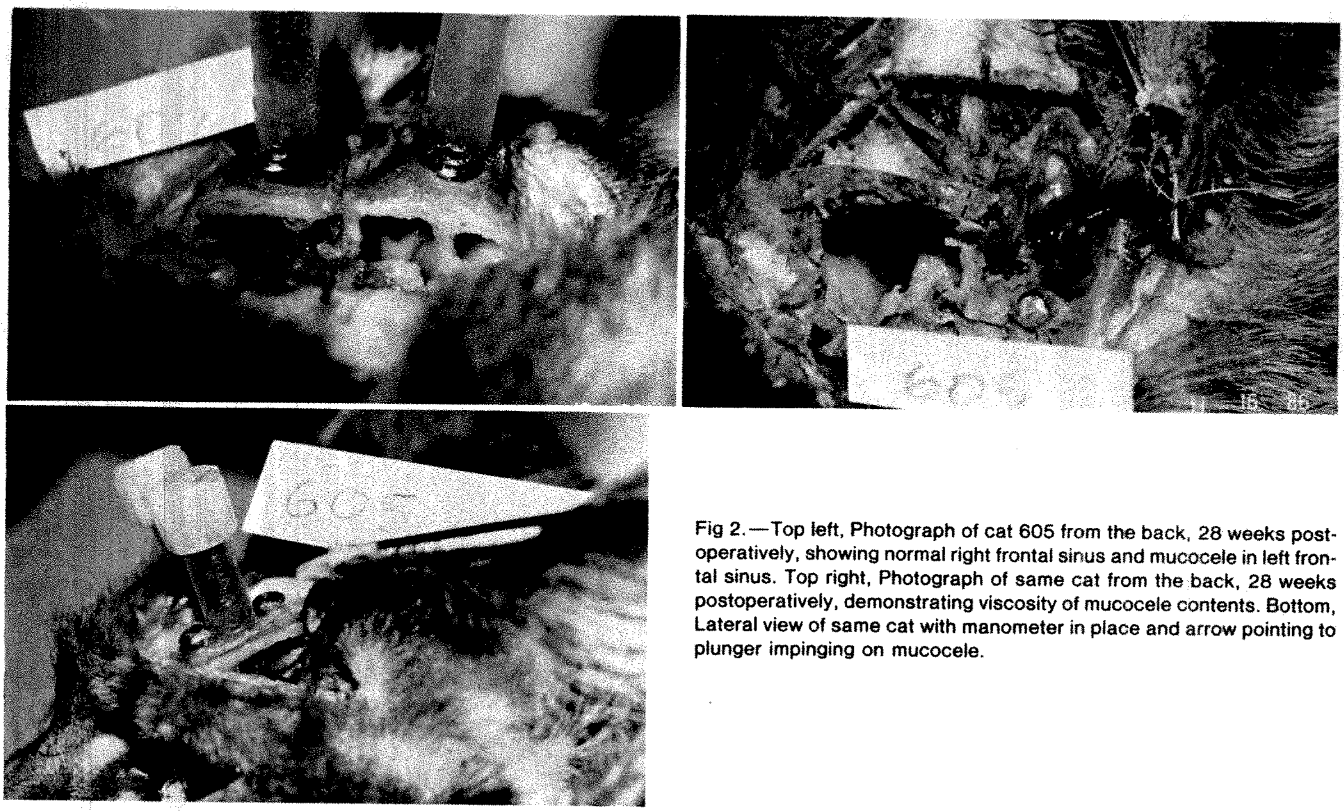

Fig 2.—Top left, Photograph of cat 605 from the back, 28 weeks postoperatively, showing normal right frontal sinus and mucocele in left frontal sinus. Top right, Photograph of same cat from the back, 28 weeks postoperatively, demonstrating viscosity of mucocele contents. Bottom, Lateral view of same cat with manometer in place and arrow pointing to plunger impinging on mucocele.

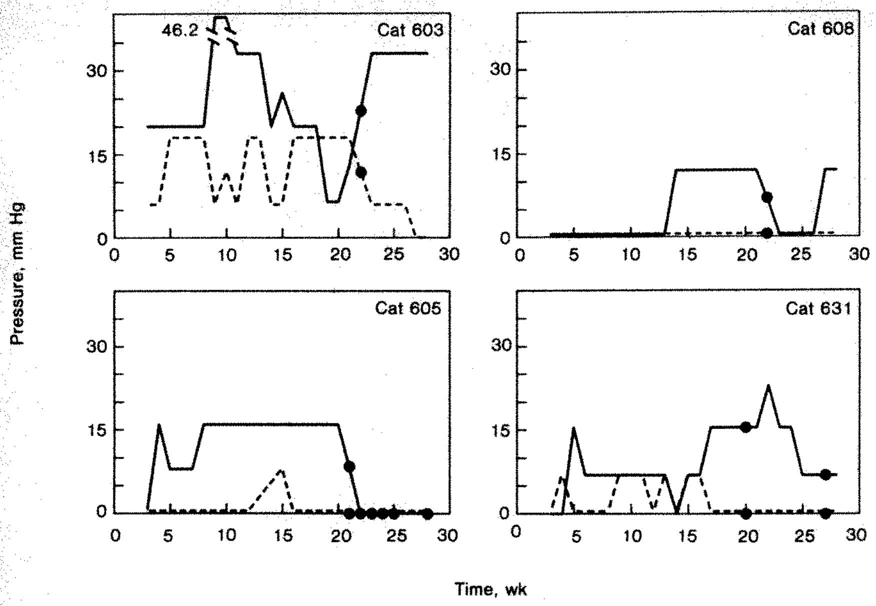

Fig 3.—Comparison of pressures in the experimental sinus (solid lines) and control sinuses (broken lines) for each of the four cats that developed mucoceles. Circles represent missing data points.

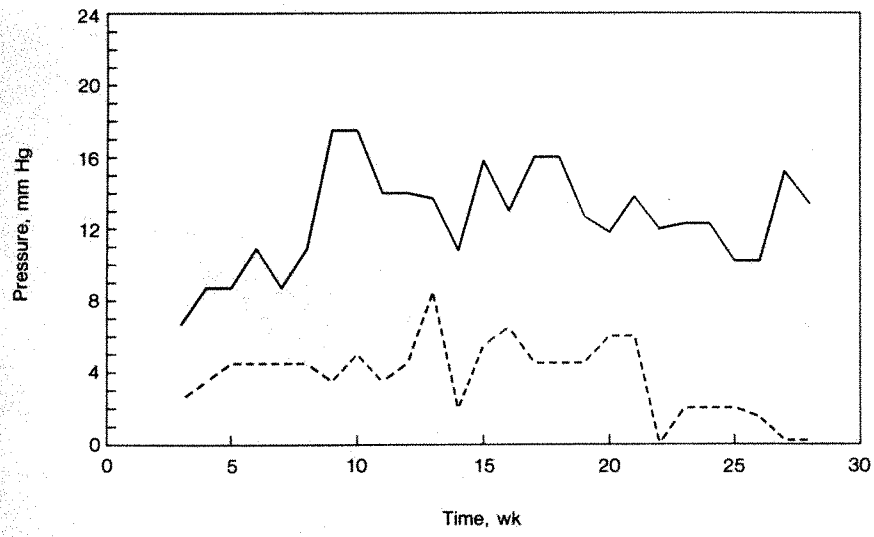

Fig 4.—Comparison of mean pressures in the experimental sinuses (solid line) with those in the control sinuses (broken line).

which gives pressure in units of dynes per square centimeter. This is converted to millimeters of mercury by the following relationship:

$$1\ \text{dyne/cm}^2 = 7.5 \times 10^{-4}\ \text{mm Hg}.$$

Blinded readings were taken weekly from all manometers. These readings began 3 weeks after implantation and continued for 26 weeks.

After the 26th reading, each cat was given a lethal intramuscular injection of ketamine hydrochloride and xylazine (Rompon). As soon as there was no response to painful stimuli, a median sternotomy was performed and the right brachycephalic trunk (which gives rise to both common carotid arteries in the cat) was cannulated with an 18-gauge dimethicone catheter. Through this catheter, Karnovski's fixative (2% glutaraldehyde and 2% paraformaldehyde in 0.1-mol/L cacodylate buffer) was infused until a small buccal mucosal incision "bled" only clear fixative.

All soft tissues were removed from the anterior aspect of the skull, and each sinus was opened and examined for evidence of mucocele. Multiple specimens of the bony sinus walls were immediately harvested and placed into Karnovski's fixative. The manometers were removed and recalibrated. The bony specimens were decalcified in Baird's[14] edetic acid for 5 months. Once decalcified, each specimen was embedded in epoxy resin and epoxy resin A (Epon-Araldite) and sectioned in 1.0-μm increments. Representative sections were stained with toluidine blue and basic fuchsin. A microscope (Olympus BH) was used to analyze the sections. Bone thickness was measured using a camera lucida attachment that projected images of the sections onto a digitizing tablet linked to an image analysis system (VIAS, Ted Pella Inc, Redding, Calif).

This study was approved by the University of California, Davis, Animal Use and Care Administrative Advisory Committee.

RESULTS

Two of the original seven cats were eliminated from the study; one was too perverse to handle, and the other repeatedly dislodged its manometers. A third cat developed no mucocele. This cat was excluded from the analysis of pressure data, but not from histologic study.

All control sinuses had a normal appearance. They contained no fluid or debris. The mucosa was thin and uninflamed. The walls of the sinuses were of grossly normal thickness. All experimental sinuses except one were filled with cystic structures containing brown, viscous, mucoid material (Fig 2). All the experimental sinuses had grossly thickened walls.

In general, the pressure in all sinuses continued to rise for the first 8 weeks after implantation of the manometers. After this, it remained roughly constant in the experimental sinuses. The control sinuses demonstrated a return toward lower pressures after the 15th week after implantation.

The highest pressure recorded from an experimental sinus was 46.2 mm Hg. The highest pressure recorded from a control sinus was 18 mm Hg. A repeated-measures analysis of variance showed that the mean pressures were significantly higher in the experimental sinuses ($F_{1,3} = 20.33$; $P = .0204$).

Figure 3 illustrates the pressures on

the experimental side for each cat compared with its control. Figure 4 shows a comparison of the mean pressures in the experimental sinuses with those in the control sinuses.

Contrary to the anticipated result, the bone of the experimental sinuses was thicker than on the control side (Fig 5). Paired *t* tests performed on log-transformed bone thickness data showed this to be true when comparing the experimental and control sides of the intersinus septum (2.16 ± 2.54 mm vs 0.17 ± 0.03 mm; $P = .0048$), as well as when comparing the anterior tables of the experimental and control sinuses (2.74 ± 1.04 mm vs 0.98 ± 0.33 mm; $P = .002$). The mucosa of the experimental sinuses was 5 to 10 times thicker than the normal mucosa in the control sinuses.

The abnormal bone was laid down in a trabecular pattern, unlike the lamellar bone of the control sinuses (Fig 6). The interstices between the trabeculae were filled with mucus, cellular debris, inflammatory cells, and occasional bacteria. None of these changes was seen in the control sinuses. Osteoclasts and osteoblasts were not found.

COMMENT

Ever since mucoceles were first described, it has been postulated that they cause pressure that erodes the bone of the sinus walls.[9-13] While it is clinically apparent on draining a mu-

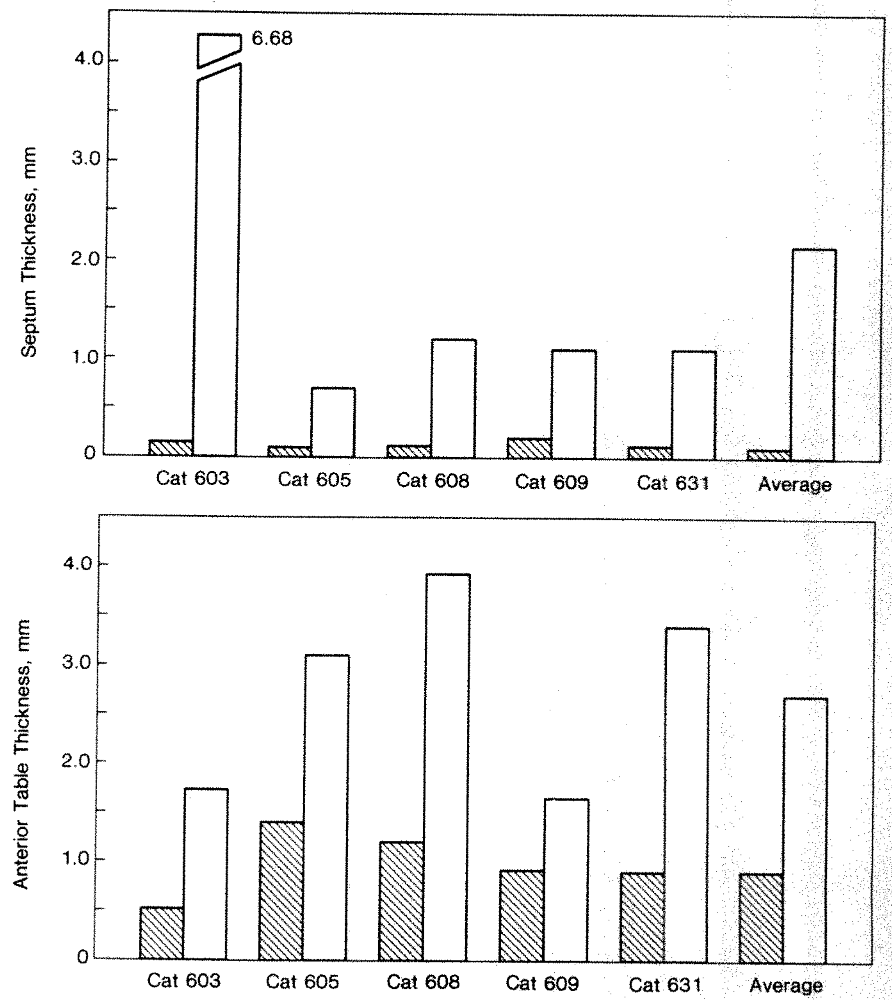

Fig 5.—Top, Comparison of the thickness of the control side of the intersinus septum (hatched bars) with the experimental side (open bars) for each cat. Bottom, Comparison of the thickness of the anterior table on the control (hatched bars) and experimental (open bars) sides for each cat.

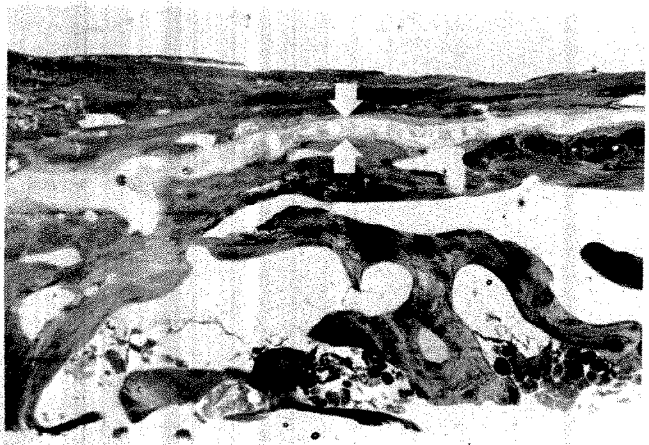

Fig 6.—Cat 609. Intersinus septum (arrows) separates trabeculated bone, representing osteoneogenesis on the side of mucocele formation (below) from normal lamellar bone on the control side (above) (hematoxylin-eosin, ×65).

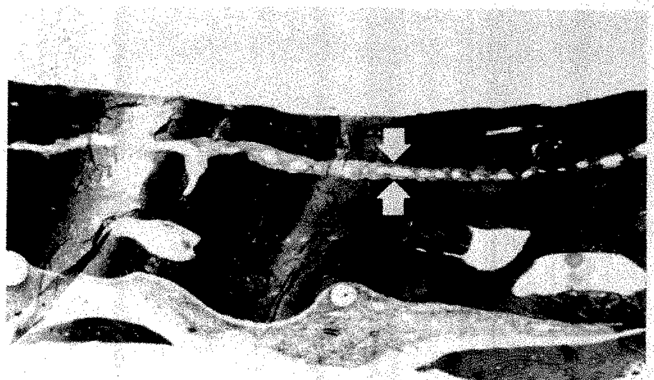

Fig 7.—Cat 631. Similar situation as in Fig 6, with the test side below the intersinus septum (arrows) and the control side above (hematoxylin-eosin, ×65).

cocele that its contents are under pressure, that pressure has never before been measured. It was not known if the pressure was high enough to cause bone erosion. Our results show that, in fact, it is. Orisek and Chole[15] showed that 4.66 mm Hg exerted by a cholesteatoma could erode bone. The mucocele pressures we measured averaged about 12.6 mm Hg and were as high as 46.2 mm Hg.

We did not, however, find bone erosion. On the contrary, we found hyperplasia of abnormal bone. Schenck[16] described remarkably similar lesions in association with bony hyperplasia when working with the canine frontal sinus. Such new bone formation was called "proliferative osteomyelitis" by Maxwell[17] because of its apparently inflammatory origin. Schuknecht and Lindsay[7] felt that proliferative osteomyelitis resulting from a mucocele was "not unusual." Osteoneogenesis in association with mucoceles is commonly seen on computed tomographic scans,[18] although it can be concomitant with osteolysis.

In humans, the erosive effects of mucoceles are seen many years after the injury. Bordley and Bosley,[3] reporting on 56 patients, noted an average of 7.5 years between the time of injury and the appearance of the mucocele. In one of their patients, the interval was 42 years. In this study, 7 months elapsed from the time of injury to sacrifice and similar periods were used by Schenk et al[6] with their dogs.

There is probably a two-stage process whereby mucoceles initially incite an inflammatory proliferative phase, which is later replaced by a pressure-induced erosive phase. The radiology literature suggests the two stages may coincide.[18]

CONCLUSION

This study was designed to measure the pressure exerted by frontal sinus mucoceles in the cat, and to document the resultant bony changes. We may conclude that the pressure exerted is high enough to cause bone erosion. In the early stages of a mucocele, however, other factors outweigh the pressure effects resulting in bony proliferation. Longer-term studies will need to be designed to delineate the interplay between the proliferative and erosive factors.

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Endoscopic Transnasal Surgery in Antrochoanal Polyp

Reda Kamel, MD

• The current treatment of antrochoanal polyp is simple avulsion of the nasal part with or without removal of the antral part. The antral part is removed through a Caldwell-Luc antrostomy, inferior meatal antrostomy, or middle meatal antrostomy. In this study, endoscopic surgery was performed in 22 cases of antrochoanal polypi where the antral part was removed through the middle meatus. Two new instruments were designed to help complete removal of the antral part of the polyp through the maxillary ostium. Some points of controversy concerning the antrochoanal polyp are discussed according to the diagnostic and therapeutic endoscopic findings. Endoscopic follow-up of these cases for periods ranging between 6 and 30 months, with an average of 20 months, showed no recurrence. It was concluded that endoscopic surgery of the antrochoanal polyp through the middle meatus could be performed as an outpatient procedure, and is safe and reliable.

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Since Killian[1] discovered the origin of the antrochoanal polyp to be from the maxillary sinus, many attempts have been made to reduce the incidence of postsurgical recurrence. Because of the risk of recurrence and resistant disease after simple avulsion, antral exploration and removal of maxillary sinus disease is generally recommended. This is usually performed through the Caldwell-Luc antrostomy; however, utilization of an inferior meatal nasoantral window[2,3] or a middle meatal antrostomy under endoscopic control[4] have also been recommended recently.

There are many points of controversy concerning the antrochoanal polyp, including the following: Is the antrochoanal polyp an absolutely solitary finding, or could it be multiple? What is the route through which the polyp passes into the nose? What is the size of the maxillary ostium? What is the site of the origin of the polyp, and its nature within the maxillary sinus? Moreover, what is the best route through which the antral part of the polyp could be removed? How does one deal with any associated pathological and/or healthy sinus mucosa?

The aim of this article is to discuss these points of controversy according to the diagnostic and therapeutic endoscopic findings, and to evaluate the feasibility of endoscopic removal of the antral part of the antrochoanal polyp through middle meatal antrostomy.

PATIENTS, MATERIALS, AND METHODS

Endoscopic removal of the antrochoanal polyp through middle meatal antrostomy was done in 22 patients. There were 12 males and 10 females. Their ages ranged between 10 and 52 years, with an average age of 25 years. The main symptom was usually nasal obstruction due to the large nasopharyngeal part of the polyp. This was unilateral in 15 patients and bilateral in 7 patients. Fourteen patients had recurrent polypi after previous simple avulsion (11 patients) and/or Caldwell-Luc procedure (3 patients).

The antrochoanal polyp was strictly unilateral and, in most of the patients, it was a single polyp. In 3 patients, two polypi could be traced coming out of the maxillary sinus and 6 patients were associated with ipsilateral ethmoid polypi.

Deviated septum was severe in 3 patients, where it was essential to perform septoplasty before endoscopic removal of the polyp. Endoscopic removal of the antrochoanal polyp was typically performed under local anesthesia with preoperative sedation. General anesthesia was used in four patients, one of whom was a child, and, in the three other patients, septoplasty was also indicated. The area anterior to the uncinate process was infiltrated with lidocaine (Xylocaine) adrenaline 2% using the 0-degree endoscope. The uncinate process was incised using a sickle knife and was then removed. The pedicle of the polyp was then infiltrated with lidocaine adrenaline 2% and then incised using a pair of forward-cutting scissors. The nasal part was easily removed either transorally when large or transnasally when reasonably small. The antral part was removed through the maxillary ostium using the upward-cutting forceps. The maxillary ostium was wide enough in most cases, but widening of the ostium was sometimes needed using the backward-cutting forceps. Suction of any retained secretions was done and the 30- and 70-degree endoscopes were used to help remove any residual intra-an-

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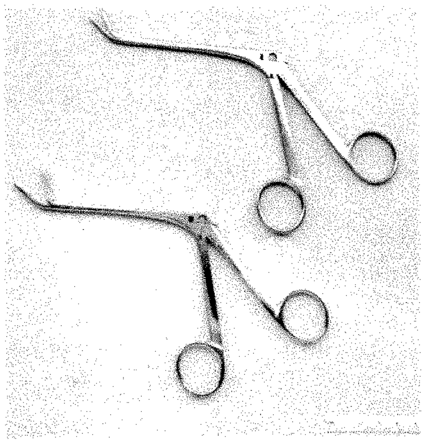

Fig 1.—The two new instruments designed to help complete removal of the antral part of the antrochoanal polyp.

tral part of the polyp, thickened mucosa, polypi, and/or cysts. Two pairs of forceps were designed to offer more length to reach all the antral walls and give a wide range of movement with a fairly sharp and firm grip (Fig 1). Care was taken to preserve healthy areas of the sinus mucosa. Ethmoidectomy was performed when indicated.

RESULTS

During endoscopic removal of the antrochoanal polyp, excision of the uncinate process was performed in only 7 patients. In the other patients the uncinate process was atrophied most probably due to pressure atrophy by the polyp. In most of the patients the nasal and nasopharyngeal part of the polyp was removed transnasally, but in 6 patients, where the polyp was rather large, it was removed transorally. In 20 patients the polyp passed through the main ostium (Fig 2). In one of these patients, where there were two antrochoanal polypi, one polyp exited the main ostium and the other an accessory ostium. In the two other patients the pedicle exited through an inferior meatal antrostomy of a previous Caldwell-Luc procedure (Fig 3). In one of these two patients the maxillary ostium was blocked by ethmoid polypi, and in the second patient the area of the maxillary ostium was obliterated by adhesions. Most of the cases were associated with a wide enough ostium to visualize and manipulate the interior of the antrum using the two new upward-cutting forceps and the 30-and 70-degree endoscopes. Only 5 patients required surgical widening of the maxillary ostium. In one patient where the maxillary ostium no longer existed due to adhesions from a previous Caldwell-Luc procedure, middle meatal antrostomy was done through these adhesions. The antral part of the polyp was cystic in only 5 patients and polypoid in 17 patients (Figs 4 and 5). In 13 patients the polyp was attached to the medial antral wall, and the remaining mucosa of the sinus was almost healthy. In the 9 other patients the antral wall was generally diseased and the origin of the polyp could not be determined precisely. Endoscopic follow-up of these patients for periods ranging between 6 and 30 months, with the average of 20 months, revealed no recurrence.

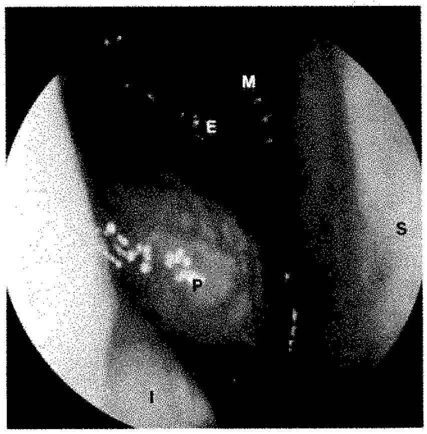

Fig 2.—Endoscopic view of right nasal cavity with 30-degree endoscope. The antrochoanal polyp (P) exiting the main maxillary ostium associated with ethmoid polypi (E). M indicates middle turbinate, I, inferior turbinate; and S, septum.

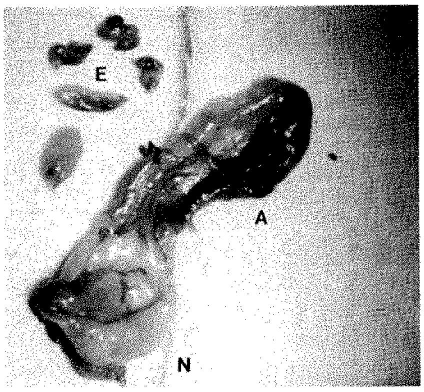

Fig 4.—The antrochoanal polyp showing a ruptured cystic antral portion (A). Associated ethmoid polypi (E) were also removed. N indicates nasal part of polyp.

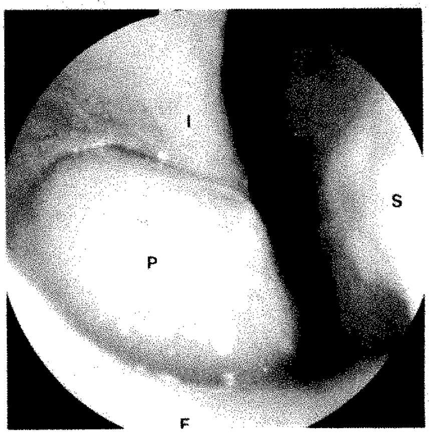

Fig 3.—Endoscopic view of right nasal cavity with 30-degree endoscope. The antrochoanal polyp (P) exiting an inferior meatal antrostomy of a previous Caldwell-Luc procedure. I indicates inferior turbinate; F, floor of nasal cavity; and S, septum.

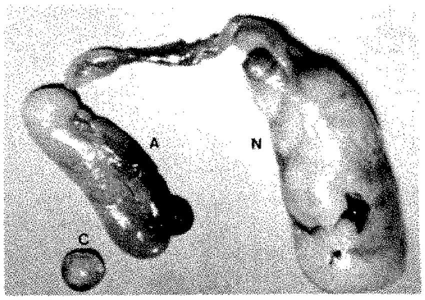

Fig 5.—The antrochoanal polyp showing a large nasal and nasopharyngeal part (N) and polypoid antral part (A). A small retention cyst (C) was also found in the maxillary sinus, and was removed.

COMMENT

In this work it was found that the antrochoanal polyp was usually a solitary finding. In 3 patients, two polypi could be traced coming out of the maxillary sinus, each with a separate pedicle and 6 patients were associated with ipsilateral ethmoid polypi. Although it was previously stated that the antrochoanal polyp is predominantly solitary,[5] some investigators reported cases with multiple antrochoanal polypi[1,6] and associated ethmoid disease.[7]

There is a controversy concerning the exit of the polyp from the maxillary sinus, whether it is through the natural maxillary ostium[2-6] or an accessory ostium.[1-8] In this study, it was found that, in most cases, the polyp passed through the main maxillary ostium. In 2 patients the pedicle was through an inferior meatal antrostomy of a previous Caldwell-Luc operation, where the maxillary ostium was blocked by iatrogenic fibrosis in 1 patient and extensive ethmoid polypi in the second.

Most of the cases seen were associated with a wide ostium at the expense of the nasal fontanelle, and only 5 patients required surgical widening to obtain a good view of the antrum. Neel[7] declared that frequently the natural ostium of the sinus is large, and it is not clear whether this is due to the presence of the stalk or whether this precedes the development of the polyp, giving a route for the antral mucosa to prolapse into the nose and form the polyp.

There is a controversy concerning the nature of the antral part of the polyp, whether it is cystic or polypoid.[1,2,8,9] In this study, the antral part of the polyp was cystic in only 5 patients and polypoid in 17 patients.

In this study, it was noticed that, in 13 patients, the polyp was attached to the medial antral wall, and the remaining mucosa was more or less healthy. In the 9 other patients the antral wall was generally diseased and the origin of the polyp could not be determined precisely. It was previously stated that the point of origin of the pedicle within the antrum appeared to vary,[10] and many investigators noticed that the maxillary sinus is often full of thickened, polypoid mucosa so that generally the site of origin within the maxillary sinus cannot be delineated.[2,10] Endoscopically the antrochoanal polyp was found by others to arise from the vicinity of the inner maxillary ostium, the posterior nasal fontanelle, and/or the maxilloethmoid angle of the maxillary sinus,[4] and was associated with healthy mucosa of the other walls of the maxillary sinus.[11]

It is generally recommended that, in order to avoid recurrence after antrochoanal polypectomy, the antral part of the polyp should be removed. There is controversy concerning the route of removal of the antral part.

Caldwell-Luc antrostomy offers a good exposure and ensures complete removal of the antral part of the polyp, as well as all the sinus mucosa.[7-12] Although the reports concerning the results of the Caldwell-Luc procedure and its modifications reported no recurrence,[7-12] in our study, 3 patients had a history of recurrence after the Caldwell-Luc procedure. Many side effects were reported after this procedure in the form of swelling of the cheek in the immediate postoperative period, long recovery time, and late postoperative sequelae, such as numbness and anesthesia of the cheek and devitalization of teeth.[13]

It was claimed that the inferior meatal antrostomy offers enough exposure of the maxillary sinus for removal of the antral part of the polyp,[7] especially after excision of the anterior part of the inferior turbinate.[3] Neel[7] reported one recurrence in 21 cases and Ophir and Marshak[3] reported no recurrence in 12 cases. On the contrary, others stated that the inferior meatal antrostomy gives poor access to the antrum for either inspection or treatment.[13]

In this study the nasal and antral parts of the antrochoanal polyp were removed endoscopically. The antral part was removed via the maxillary ostium. Any associated pathologic findings in the maxillary sinus in the form of polypi, cysts, or thickened unhealthy mucosa were removed. Two pairs of forceps were designed to offer length to reach all the antral walls and give a wide range of movement with a fairly sharp and firm grip. Endoscopic follow-up of these cases for periods ranging between 6 and 30 months, with an average of 20 months, revealed no recurrence.

Although it was previously stated that the disease if eliminated eventually by polypectomy combined with curettage of the antrum to remove almost all the sinus mucosa,[2,3] using the endoscope ensures complete removal of the polyp and any associated pathologic findings through the maxillary ostium and offers preservation of the healthy sinus mucosa. This is good for later epithelialization and mucociliary clearance, and is not followed by recurrence.

In conclusion, endoscopic surgery in antrochoanal polyp through the middle meatal antrostomy offers the following advantages: it ensures complete removal of the antral part of the polyp and diseased mucosa without the need to perform a Caldwell-Luc antrostomy or inferior meatal antrostomy, it offers preservation of the healthy sinus musoca for later epithelialization, any associated ethmoid polypi could be detected and removed simultaneously, and it could be performed in children without harm to the permanent dentition.

Endoscopes, instruments, and photodocumentation equipment for this study were provided by Karl Storz.

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Detection and Typing of Papillomavirus DNA in Formaldehyde-Fixed Paraffin-Embedded Tissue

Janet L. Brandsma, PhD; Annika J. Lewis; Allan Abramson, MD; M. Michele Manos, PhD

• **Clinical specimens from nine patients with papillomatosis of the vocal cords and three patients with vocal cord polyps were evaluated for the presence of human papillomavirus (HPV) DNA using two complementary molecular hybridization techniques. In one method, involving polymerase chain reaction (PCR) amplification, HPV DNA sequences were replicated in vitro from tissue DNA extracted from paraffin sections prior to hybridization. Polymerase chain reaction amplification was compared with the standard method of Southern blot hybridization. Results of the two techniques for all nine laryngeal papillomas agreed completely: five patients harbored HPV type 6 and four HPV type 11. Both PCR amplification and Southern blot hybridization found two of the three polyps to be free of HPV infection, while PCR detected HPV type 18 in one polyp specimen that was reported negative by Southern blot hybridization, suggesting a greater sensitivity of PCR. Our results demonstrate that PCR amplification is as reliable and at least as sensitive as Southern blot hybridization. Moreover the PCR technique opens the way to the undertaking of a whole variety of retrospective studies using formaldehyde-fixed paraffin-embedded tissues.**

(*Arch Otolaryngol Head Neck Surg.* 1990;116:844-848)

Application of Southern blot hybridization (SBH) has been crucial to our understanding of the involvement of human papillomavirus (HPV) in laryngeal disease. It was instrumental in discovering the etiologic linkage between infection by certain types of HPV and laryngeal papilloma,[1] in first bringing the phenomenon of latency to light,[2] and in uncovering various associations of HPV-related sequences with verrucous carcinoma of the larynx[3,4] and squamous cell carcinomas of the larynx, tongue, and oral cavity.[5-10] The SBH technique is sensitive to the detection of less than one copy of HPV per 10 cells, although a minimum of 10^4 to 10^5 cells is required to detect low levels of HPV.[11] Examination of the restriction pattern, a kind of fingerprint of the viral type, proves diagnostic of the specific HPV present. The major disadvantage of the SBH procedure is that it requires tissue to be collected and frozen quickly after surgical excision.

Detection of HPVs in clinical materials has been problematic. There is no laboratory method to propagate the virus. No antibodies are available to detect viral antigens in most tissues. The commercially available anticapsid antibody reacts specifically with structural antigen in very highly differentiated epithelial cells actively replicating virus.[12] Laryngeal papillomas are often capsid-antigen negative,[1,12,13] and squamous cell carcinomas are nearly universally so.[12]

The availability of a methodology that could be readily applied to routinely processed formaldehyde-fixed, paraffin-embedded tissues would serve greatly to open up a variety of laboratory and epidemiologic studies.

This study reports that the new molecular technique known as the polymerase chain reaction (PCR)[14-18] is as reliable and at least as sensitive as SBH for the evaluation of human laryngeal specimens. Moreover, PCR amplification can use as its substrate DNA that has been extracted from

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paraffin sections of formaldehyde-fixed tissue blocks.

MATERIALS AND METHODS

Selection of Clinical Material

A retrospective study was performed using tissue samples from patients surgically treated in the Department of Otolaryngology at Long Island (NY) Jewish Medical Center between 1985 and 1988. Nine patients with papillomatosis of the vocal cords—presumably HPV positive—and three patients with vocal cord polyps—presumably HPV negative—were chosen. All specimens had been divided at the time of surgery. Part of each lesion had been fixed in neutral buffered 3.7% formaldehyde solution (formaldehyde-fixed) and embedded in paraffin. The histologic features were evaluated in the Department of Pathology. Another part of each lesion had been immediately frozen in liquid nitrogen. The PCR analysis was performed on coded samples in a blinded fashion.

Southern Blot Analysis

Tissue DNAs were prepared and blotted as described.[6] Stringent hybridizations were performed to a probe of HPV type 11, 16, or 18. Each HPV DNA had been gel purified from plasmid and labeled with phosphorus 32 by the random prime method[19,20] to specific activities of greater than 10^9 cpm/μg.

Preparation of Paraffin-Embedded Samples for PCR

Sections (5 μm) of various biopsy samples were sliced and placed in 1.5-mL microfuge tubes. Care was taken to avoid cross-contamination of samples: the microtome blade and all supplies that contacted the sample were cleaned with ethanol between specimens. Other precautions taken to avoid false-positives are detailed in reference 21. The sections were prepared as described.[18] An improved method for extraction of paraffin-embedded samples has recently been detailed.[21]

PCR Amplification and Analysis of PCR Products

The heat-stable enzyme *Taq (Thermus aquaticus)* polymerase (Perkin-Elmer, Cetus Corp, Emeryville, Calif) was used in the amplification reactions.[17] Amplifications with HPV-L1 consensus primers MY11 and MY09 were performed as described previously.[18,22] Dot-blot hybridizations with phosphorus 32-labeled generic and type-specific oligonucleotide probes were performed as previously described.[18,21]

RESULTS

The general scheme for the PCR is shown in Fig 1. In the enzymatic PCR, DNA polymerase travels along single-stranded (denatured) DNA, incorporating correct bases to reproduce double-stranded molecules as it proceeds. The activity of the DNA polymerase is directed by short stretches of about 20 bases, called *primers*. The primers, in our case specific segments of HPV DNA, are first bound to denatured total DNA that has been extracted from each laryngeal specimen. The polymerase then undertakes its copying activity at the single-stranded DNA sequence marked by the binding of one primer; the complementary strand of DNA is copied from a second site marked by the other primer, some 200 to 500 bases away. Amplification of the HPV DNA sequences flanked by these two primers is then accomplished. Only if HPV DNA is present does the reaction proceed toward the formation of the desired product. Approximately 40 cycles of the copying procedure are undertaken, resulting in an exponential amplification of the target sequence. For our sample DNAs, potentially harboring HPVs, the consensus primers MY11 and MY09 would flank a region of the viral genome (in L1), approximately 450 base pairs long, the ends of which are well conserved among all the genital HPVs.

Figure 2 shows that all nine of the papillomas (patients 1 through 9) and one of the three polyps (patient 11) were positive. Amplification of each of these samples by PCR resulted in the synthesis of a fragment approximately 450 base pairs long (Fig 2, top). To confirm that these amplified sequences were HPVs, a Southern blot of a second aliquot of each was hybridized to a generic probe specifically designed to identify HPV sequences of those virus types that infect the genital and respiratory tracts (data not shown). The generic probe hybridized to each sample that had displayed an amplified product but to neither of the two samples that had failed to amplify.

We next wished to define the type of HPV present in each of the lesions. Replicate dot blots were hybridized separately to oligonucleotides specific for HPV type 6, 11, 16, or 18, or for the generic probe (Fig 2, bottom). In confirmation of the results shown in the top of Fig 2, the generic probe hybridized to amplified samples from patients 1 through 9 and 11 and not to those of patients 10 and 12. Results demonstrated the presence of HPV-6 (patients 2, 3, 5, 6, and 7) or HPV-11 (patients 1, 4, 8, and 9) in each of the papillomas and of HPV-18 in one of the polyps (patient 11).

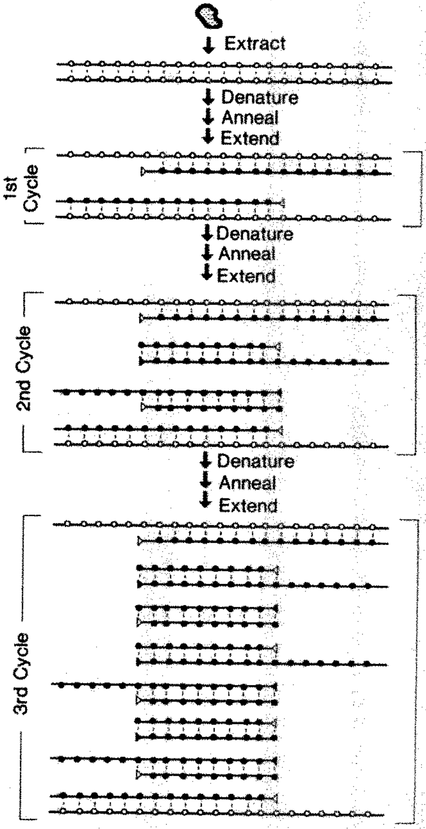

Fig 1.—The polymerase chain reaction. Open circles represent sample (target) DNA. Closed circles represent DNA synthesized in the polymerase chain reaction. Small triangles at the ends of the newly synthesized DNA represent the primers. Double-stranded DNA is extracted from paraffin sections for use as template. It is denatured, ie, rendered single-stranded, into complementary strands. Primers bind to denatured template DNA and direct the activity of *Taq* (*Thermus aquaticus*) polymerase; *Taq* extends the length of the primer by adding bases complementary to the template strand. The result of the first cycle of extension, or "amplification," is 2^1 copies of synthesized DNA; the second cycle, 2^2 copies; the third, 2^3 copies, and so on. Cycles are repeated 40 times, resulting in some 2^{40} copies of newly synthesized target DNA from one original copy.

The standard molecular technique for the detection of HPV sequences in laryngeal tissues is SBH. This tech-

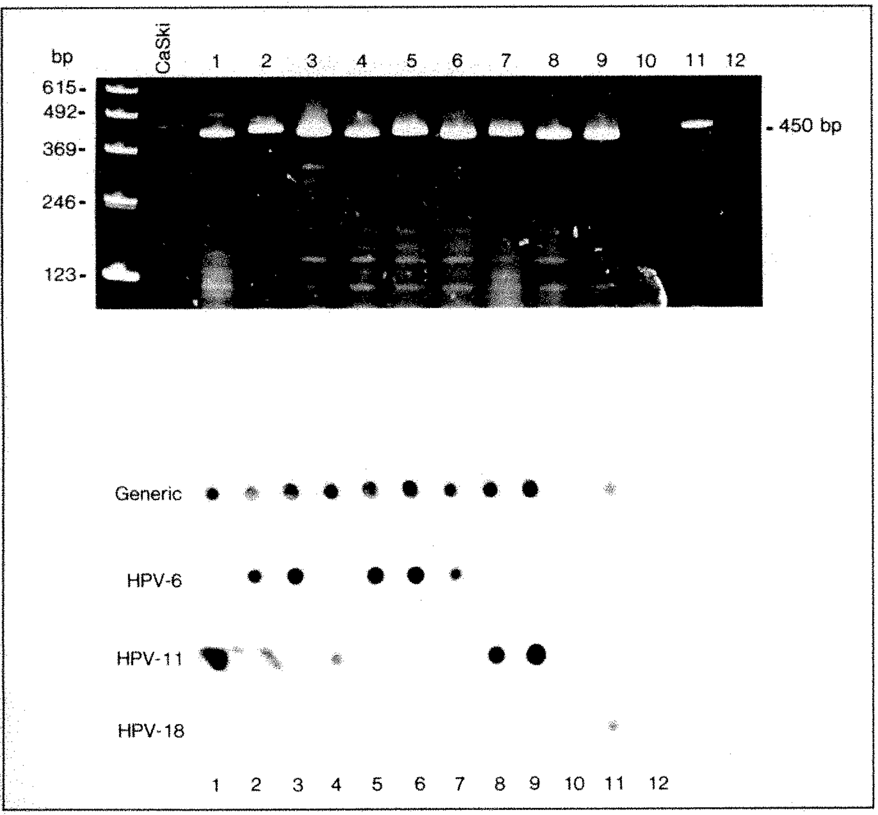

Fig 2.—Evaluation of human papillomavirus (HPV) status using polymerase chain reaction (PCR). A percentage of each amplification reaction was analyzed by gel electrophoresis (top) or dot-blot analysis (bottom). Top, The PCR products were separated in a 7% polyacrylamide gel, stained in ethidium bromide, and photographed under ultraviolet light. Each lane reflects 5% of a PCR reaction. A 123-base pair (bp) ladder, shown in the first lane, was used as a size marker. DNA from the CaSki cell line, harboring HPV-16, served as positive control. Bottom, Replicate dot blots were prepared and hybridized with type-specific and generic probes denoted at the left of each filter. Each dot reflects 3% of the amplification reactions. No hybridization was detected with probes specific for HPV-16 or HPV-33; these data are not included.

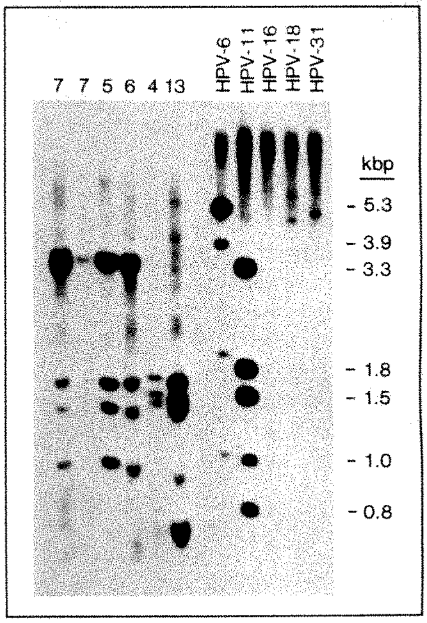

Fig 3.—Detection of human papillomavirus (HPV) using standard Southern blot hybridization. DNAs from laryngeal papilloma biopsy specimens were cleaved with *Pst* I, separated in an 0.8% agarose gel and hybridized to an HPV-11 probe. Two separate biopsy specimens from patient 7 are shown; HPV DNA was more abundant in the one in the first lane than in the one in the second lane. All of the fragments of HPV-6a were present in the one in the second lane, as seen on longer exposure (not shown). Papilloma tissue from patient 13 was not analyzed by PCR. Reference standards of *Pst* I-cleaved recombinant HPV DNAs, mixed with aliquots of *Pst* I-cleaved human tonsil DNA, are on the right, and the sizes of HPV-6- and HPV-11-specific fragments are marked; kbp indicates kilobase pairs.

nique was applied to DNAs independently isolated from samples of the papillomas and polyps included in this study. Figure 3 displays the results of a representative SBH of four of the vocal cord papilloma DNAs to an HPV-11 probe. Since the DNA sequences of HPV-6 and HPV-11 are 85% homologous, the HPV-11 probe detects the presence of HPV sequences of either type. Specimens from patients 5, 6, and 7 harbor HPV-positive *Pst* I fragments of 3.8-, 1.7-, 1.4-, and 1.0-kilobase pairs, the restriction pattern diagnostic of HPV-6a.[23] The specimen from patient 4 exhibits HPV-positive *Pst* I fragments of 1.8-, 1.6-, 1.5-, and 1.0-kilobase pairs and thus contains HPV-11a.[23]

Once both sets of molecular analyses were completed, the results were decoded and demonstrated perfect correlation, with one exception (Table). All of the laryngeal papillomas contained HPV-6 or HPV-11, as was expected according to previously published findings.[1,2,23] Significantly, in making the distinction between HPV-6 and HPV-11, there was complete agreement between the two methods.

None of the polyps were found to harbor HPV type 6, 11, or 16. Using the PCR, however, one polyp showed clear evidence of the presence of HPV-18-related DNA. In contrast, SBH failed to detect HPV-specific signals in this tissue with any of the viral types used as probes, even on subsequent hybridization.

COMMENT

The involvement of papillomaviruses in laryngeal disease is important to understand, since the larynx is well known for its susceptibility to HPV infection. Knowledge concerning the association of HPVs with laryngeal diseases has been derived mostly using SBH. However, since SBH does not generally apply to formaldehyde-fixed, paraffin-embedded tissues available in pathology departments, the involvement of HPV in laryngeal diseases using this technique is limited to prospectively collected specimens. Retrospective studies are not possible.

To facilitate the understanding of HPV infection and its role in carcinogenesis of the larynx, we sought to improve on current methods of detection. Thus we employed the PCR technique to evaluate the presence and type of HPV genetic information in the DNA from stored paraffin blocks of human laryngeal tissue. The use of PCR to detect HPVs in paraffin-embedded tissues from other sources has been

Correlation of Molecular Findings for Human Papillomavirus (HPV) Between Southern Blot Hybridization (SBH) and Polymerase Chain Reaction (PCR)

Lesion	Patient No.	BH Result	PCR Result	Agreement
Papilloma	2	HPV-6	HPV-6	Yes
Papilloma	3	HPV-6	HPV-6	Yes
Papilloma	5	HPV-6	HPV-6	Yes
Papilloma	6	HPV-6	HPV-6	Yes
Papilloma	7	HPV-6	HPV-6	Yes
Papilloma	1	HPV-11	HPV-11	Yes
Papilloma	4	HPV-11	HPV-11	Yes
Papilloma	8	HPV-11	HPV-11	Yes
Papilloma	9	HPV-11	HPV-11	Yes
Polyp	10	Negative	Negative	Yes
Polyp	12	Negative	Negative	Yes
Polyp	11	Negative	HPV-18	No

described.[18] Polymerase chain reaction, an adaptation of the natural process whereby DNA replicates, is a recently developed molecular technique that permits synthetic amplification of regions of interest in DNA of complex samples (Fig 1). For example, in our study, we amplified HPV DNA from among all cellular DNA sequences extracted from a dozen different laryngeal tissues (Fig 2). The power of the PCR technique becomes obvious when one considers that at, for instance, one copy per cell, an HPV genome would represent 0.002% of total cellular DNA. It is because of specific amplification of particular targeted regions that PCR can distinguish among the genomes of HPV types 6, 11, 16, and 18. Its specificity is thus similar to that of SBH. The results of our study clearly demonstrate that this PCR-based method specifically detects the very same types of HPV as does SBH when both techniques report the presence of HPV (Fig 2, bottom, and Table).

In addition, the detection of HPV-18 sequences by the PCR method in a tissue specimen that was found to be negative for HPV by SBH indicates an even greater sensitivity of PCR. The significance of this finding remains unclear. The patient involved was a 59-year-old woman who presented with hoarseness in March 1986. Clinical evaluation revealed bilateral vocal cord polyps. The patient had no evidence of any benign or malignant neoplasms, including those that might be caused by HPV. Biopsy specimens of the right and left vocal cords obtained for histologic evaluation confirmed the presence of typical vocal cord polyps. No koilocytosis or other microscopic feature of HPV infection was found. She was treated using the carbon dioxide laser. At 40 months of follow-up, her larynx was normal, without any clinical evidence of papilloma.

Laryngeal polyps have previously been found to be negative for papillomavirus sequences, although two other patients who had polyps on the true vocal cords were found to harbor HPV-11a in their false cords, a finding that was interpreted to indicate the likelihood of latent infection.[6] The detection of HPV-18 in a head and neck specimen is particularly interesting in view of the fact that this type of HPV has rarely been reported in such tissues. Because hybridization of the HPV-18 type-specific probe to this PCR product was weak, this polyp may harbor an HPV that is related but not identical to HPV-18. In any case, this finding should alert us to the possibility of HPV involvement, either etiologically or as a passenger, in certain laryngeal polyps. Alternately, this finding may reflect latency either in the polyp itself or in adjacent normal epithelium also present in the tissue section. Human papillomavirus latency in the larynx has been documented.[2,6]

There are obviously certain types of studies for which the PCR would not be applicable. The technique does not allow localization of viral sequences to specific cells, as does in situ hybridization. However, in the HPV system, the latter method is only sensitive to an estimated 25 copies of HPV per cell.[24] Cells that are not replicating virus would prove negative by in situ techniques. The sensitivity of PCR depends not on the copy numbers of HPV per cell, but rather on the total amount of HPV DNA present. Thus, the PCR method described here can detect a total of fewer than 100 copies of HPV[18]; the HPV genomes can be concentrated in just a couple of cells or dispersed unevenly throughout millions of cells. Southern blot hybridization provides additional information about the individual restriction fragments present. However, SBH requires fresh tissue, and that fact alone precludes its use for all but prospective studies with investigators who have the capacity to collect and freeze tissue samples immediately after surgical excision. Furthermore, SBH is probably less sensitive than PCR, as indicated both by one of our results (the HPV-positive polyp) and other studies.[18]

The sensitivity, specificity, and applicability of PCR to material stored in the pathology department suggests to us a wide range of applications. We have already shown (Table) how the technique may be used to detect specific HPV types. This is obviously of use in clinical and epidemiologic studies. The PCR technique would be useful for the study of diseases of low incidence such as inverted papillomas of the nose, for which the prospective collection of appropriate specimens would require years.

Another rare disease, for which there is evidence of papillomavirus involvement, is verrucous carcinoma of the larynx.[3,4] On receiving this diagnosis, the clinician is faced with organizing a treatment plan. Polymerase chain reaction amplification can be applied to the formaldehyde-fixed tissue at this time to analyze HPV status on a retrospective basis. If viral genomes are found, we believe that radiotherapy should not be given unless the potential consequences are fully explained to the patient.[4]

The PCR method should enable more detailed study of the relationship of HPVs to squamous cell carcinomas and other disease states of various sites in the head and neck. The carcinogenic effect of HPV in squamous cell carcinomas is believed to be mediated through cofactors, including radiation. For example, it has been hypothesized that HPV was etiologically involved in the development of squamous cell carcinoma in patients who developed cancer of the larynx 6 to 22 years after radiation therapy for laryngeal papillomas.[25,26] The only way to approach such questions is through the use of archival materials, since radiation therapy is no longer employed for the treatment of laryngeal papillomas. The PCR technique opens the way to finding out whether these patients' cancers do in fact harbor HPV sequences.

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Granuloma Faciale

Comparison of Different Treatment Modalities

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• **Granuloma faciale is an uncommon cutaneous condition characterized by brownish-red macules, papules, nodules, and plaques. Separate areas of granuloma faciale involving the nasal skin of a 32-year-old man were treated using electrosurgery, carbon dioxide laser, and dermabrasion. All modalities provided good cosmetic and functional outcomes. The relative advantages and disadvantages of each technique are presented.**

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Granuloma faciale is an uncommon cutaneous disorder characterized by brownish-red macules, papules, nodules, and plaques. It most commonly occurs on the face and frequently is localized to the skin of the nose. Although the cause of granuloma faciale is unknown, there is evidence that it may represent a localized form of chronic hypersensitivity vasculitis.[1]

Numerous physical modalities have been suggested as treatment for this condition. These include the use of both the carbon dioxide (CO_2)[2] and argon laser,[3] surgical excision,[4] dermabrasion,[5] superficial ionizing radiation,[4] ultraviolet light and topical psoralen,[6] cryosurgery,[7] and electrodesiccation.[4] While studies concerning each modality have yielded satisfactory results, comparison studies are not available because of the rarity of the disease. To evaluate and compare the therapeutic effects of several physical modalities in the treatment of granuloma faciale we present a patient in whom separate areas of granuloma faciale were treated using dermabrasion, the CO_2 laser, and an electrosurgical device.

REPORT OF A CASE

A 32-year-old man first noticed the onset of red-brown facial lesions on his nose and cheeks 10 years earlier. The lesions became more raised and nodular with time (Fig 1). Histologic examination confirmed the presence of granuloma faciale (Fig 2). The patient was taking no medications and was otherwise in good health. Despite treatment with oral dapsone and intralesional and topical steroids, the lesions continued to enlarge. Because of unresponsiveness to medical management, surgical consultation was obtained. After field block anesthesia with 1% lidocaine and epinephrine 1:100 000, a nodular area of granuloma faciale located on the left nasal ala was treated with an electrosurgical machine using a diamond loop set with a combination cut and coagulation current. An effort was made to create a partial thickness defect that would establish the normal contour of the nose. A nodular lesion on the right ala was treated with a CO_2 laser in the continuous discharge mode. A power setting of 7 W with a spot size of 0.2 mm gave a power density of 23 000 W/cm². Overlapping passes were made with the CO_2 laser over the unwanted tissue in an attempt to vaporize tissue. The resultant char was intermittently removed using cotton swabs soaked in 3% hydrogen peroxide. Tissue was repeatedly vaporized until the created wound was even with the surrounding tissues. Finally, dermabrasion was used to remove a slightly elevated lesion at the junction of the nasal tip and the left nasal bridge. A diamond fraze wheel was used and the end point of treatment was judged to be the fine frayed collagen present in the upper reticular dermis. Approximately 15 minutes each were needed to treat the dermabrasion and electrosurgically treated sites, while 45 minutes was needed to perform the laser surgery. Immediately following treatment (Fig 3) a sterile dressing consisting of a hydrocolloid membrane was applied to all three surgical wounds. This was replaced after 24 hours by daily cleansing with 3% hydrogen peroxide followed by dressings of an antibiotic ointment and an adhesive bandage.

On follow-up examination the dermabrasion-treated nasal tip site had healed within 2 weeks. The appearance of the patient's nose at 6 weeks (Fig 4) revealed complete healing of the alar lesions without discernible scar, residual granuloma faciale, or hyperpigmentation. The side treated by CO_2 laser and the area treated with dermabrasion were more evenly textured when compared with the side treated with the electrosurgical apparatus. There

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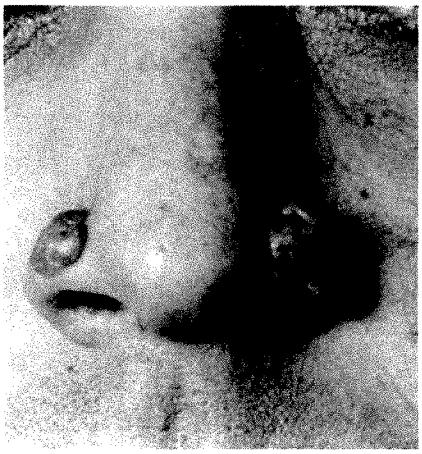

Fig 1.—Nodular lesions of granuloma faciale are present before treatment on both nasal ala. A slightly raised lesion is located at the junction of the nasal tip and the left nasal bridge. Macular lesions of granuloma faciale are seen on both cheeks.

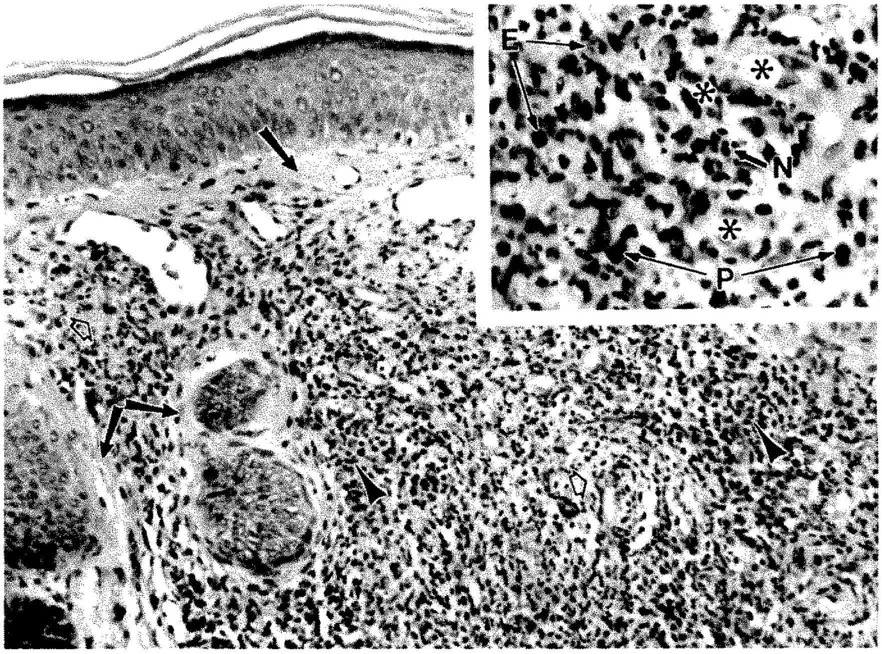

Fig 2.—A dense mixed inflammatory cell infiltrate spares a zone beneath the epidermis and around adnexal appendages (arrows). Neutrophils, nuclear fragments, and scant eosinophilic fibrinoid material are found around and obscuring small dermal vessels (open arrows). Eosinophils, plasma cells, and lymphocytes are found at the periphery of these foci (arrowheads). Inset, Asterisks indicate capillaries; N, neutrophils and nuclear debris; E, eosinophils; and P, plasma cells.

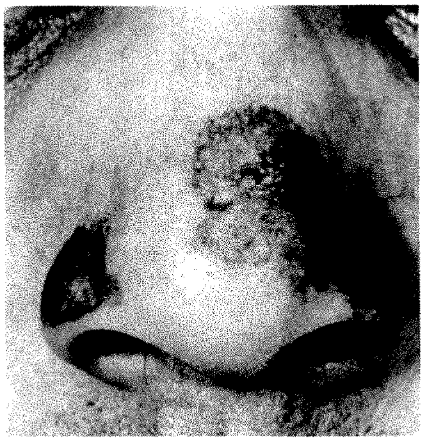

Fig 3.—Immediate postoperative appearance of the treated areas. The left alar lesion was treated with an electrosurgery apparatus, the right alar lesion was treated using a carbon dioxide laser and the nasal tip / bridge lesion was dermabraded.

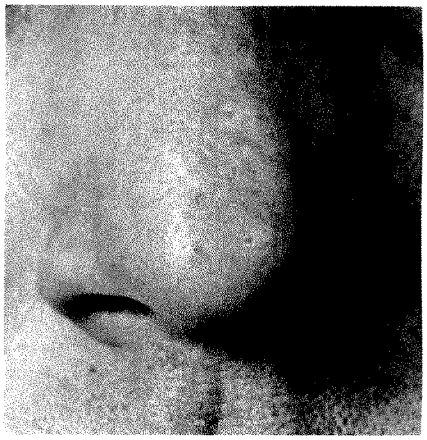

Fig 4.—Postoperative appearance of the treated areas at 6 weeks.

was no difference in healing time between the two alar lesions. The patient reported minimal pain postoperatively for all sites. He also noticed significantly more drainage from the alar lesions than the dermabraded area during the healing period. Follow-up at 1 year has detected several areas of recurrent granuloma faciale in both alar sites, which have necessitated touch-up treatments. Macular lesions of granuloma faciale located on each malar area have been well controlled with topical corticosteroids.

COMMENT

Forty years ago granuloma faciale emerged as a separate clinical entity from a broad group of eosinophilic granulomas of the skin because of its characteristic morphology, anatomic location, and histopathologic appearance. Most lesions are soft or moderately firm papules, nodules, or plaques that are red-brown in color. The general health of the patient is usually unaffected. Histologic examination demonstrates a dense polymorphous cellular infiltrate involving the upper two thirds of the dermis. The cellular infiltrate consists of lymphocytes, plasma cells, eosinophils, and histiocytes. A characteristic subepidermal grenz zone separates the infiltrate from the epidermis (Fig 2).

Medical treatments suggested for use in granuloma faciale include gold and bismuth injections,[4] oral colchicine,[3] isoniazid,[4] corticosteroids (topical,[4] intralesional,[8] and systemic[4]), potassium arsenite,[4] testosterone,[4] antimalarials,[4] and dapsone.[9] Most medical therapies are variably successful and no controlled trials are available because of the rarity of the condition. When medical therapy is ineffective, surgical treatment using a number of physical modalities is often contemplated.

Laser therapy is one of the newer physical modalities suggested as treatment for a number of benign cutaneous conditions, including granuloma faciale. The CO_2 laser uses an invisible beam of light located in the nearinfrared spectrum to nonselectively vaporize tissues with pinpoint precision. Advantages over use of electrosurgical instruments include less bleeding, less postoperative pain, increased precision, and less subclinical spread of damage to tissue during surgery.[2] Electrosurgery has advantages of being less expensive and more readily available. Healing times are believed to be longer for the CO_2 laser-produced wounds as compared with electrosurgical wounds.

Our patient had similar, separate nodular nasal alar lesions of granuloma faciale treated using an electrosurgical machine and the CO_2 laser. A separate slightly elevated patch of granuloma faciale located at the junction of the nasal tip and left nasal bridge was treated using diamond frase dermabrasion. All physical modalities provided good cosmetic and functional outcome. The side treated by CO_2 laser and the area treated with dermabrasion were more evenly textured when compared with the side treated with the electrosurgical machine. Healing time was similar between the electrosurgical and the CO_2 laser sides, while the dermabrasion area healed much more quickly. Postoperative pain was minimal and did not differ significantly for each of the three areas. Bleeding, while minimal in all areas, was less with the CO_2 laser–treated side and most over the dermabraded area. The procedure performed with the CO_2 laser took more than twice as much time when compared with the dermabrasion and electrosurgical procedures. One-year follow-up of our patient has shown small amounts of granuloma faciale recurring in treated areas and we anticipate that yearly touch-up treatments will be needed.

We conclude that careful selection of physical modalities to match the anatomic and physical characteristics of various lesions of granuloma faciale will give optimal results. Partial-thickness wounds of the alar groove and ala have been shown to heal with good results as long as the underlying cartilaginous framework is intact.[10] The manner in which these wounds are created is probably less important than the anatomic location. Dermabrasion creates a partial-thickness wound at the upper dermal layer of the skin that generally heals without scarring. This modality seems best for anatomic areas that are not favorable to second intention healing and best for macular or slightly raised lesions of granuloma faciale. It has been noted previously by other investigators that dermabrasion will not remove a nodule or dense plaque of granuloma faciale.[5] Although not emphasized in previous studies, slow recurrence of granuloma faciale in areas of previous treatment may necessitate periodic touch-up procedures.

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Persistent Stapedial Artery Supplying a Glomus Tympanicum Tumor

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• Vascular anomalies of the middle ear are extremely rare. The most common anomaly is a persistent stapedial artery. This artery is important clinically because of the risk of profuse bleeding during middle ear surgery. We describe a 26-year-old woman with a glomus tympanicum tumor. The blood supply to the tumor was from a persistent stapedial artery. A preoperative angiogram supported this finding by demonstrating a small vessel originating from the anterior branch of the middle meningeal artery as the major vascular supply to the tumor. To our knowledge, this is the first case report of a glomus tympanicum tumor vascularized by a persistent stapedial artery that was suggested by angiography and confirmed intraoperatively. To better understand this anomaly, we review the embryological development of the stapedial artery and discuss its clinical significance.

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Vascular anomalies of the middle ear are extremely rare. The most common vascular anomaly is a persistent stapedial artery, with an incidence of 1 in 5000 to 10 000 people.[1] This artery is important clinically because of the risk of sudden profuse bleeding developing during procedures involving mobilization and instrumentation of the stapes. When fully developed, the stapedial artery has a dorsal branch that is incorporated into the anterior branch of the middle meningeal artery and a ventral branch whose common trunk becomes recognizable as the proximal stem of the middle meningeal artery. It is apparent that the stapedial artery takes an important part in the embryological development of the middle meningeal artery. To better understand this anomaly we will review the embryological development of the stapedial artery and present the first documented case report (to our knowledge) of a patient with a glomus tympanicum tumor vascularized by a persistent stapedial artery that was demonstrated angiographically and confirmed intraoperatively.

REPORT OF A CASE

A 26-year-old woman presented with a 2-year history of pulsatile tinnitus and decreased auditory acuity in her right ear. Physical examination revealed a bulging right posterior tympanic membrane. Her audiogram showed a 40-dB conductive hearing loss. A computed tomographic scan of the temporal bone (Fig 1) showed an abnormal soft-tissue opacification in the right middle ear cavity and right mastoid air cells. There was no evidence of an enhancing tumor in the region of the jugular bulb or skull base. Arteriography was performed (Fig 2) and demonstrated a vascular blush supplied by a vessel originating from the right middle meningeal artery. Selective embolization of the proximal anterior branch of the middle meningeal artery was accomplished by injection with absorbable microfibrillar collagen (Avitene) and radiopaque contrast mixture. The patient underwent excision of a right glomus tympanicum tumor through a combined transcanal-transmastoid approach. The tumor was found in the posterior superior quadrant of the mesotympanum surrounding all three ossicles. During tumor removal, a persistent stapedial artery was identified penetrating the floor of the middle ear cavity, coursing through the tumor and the stapedial obturator foramen. The blood supply to the tumor was derived from this artery.

COMMENT

The persistent stapedial artery is a primitive vessel, a branch of the internal carotid artery that rarely persists into adulthood in humans. In other species, rodents for example, a stapedial artery is present in all adults. When present, the artery enters the middle ear in the anteroinferior quadrant through a narrow osseous channel.[2] It perforates the floor of the tympanic cavity and passes over the promontory and through the crura of the stapes, close to the anterior crus, where it enters the facial canal

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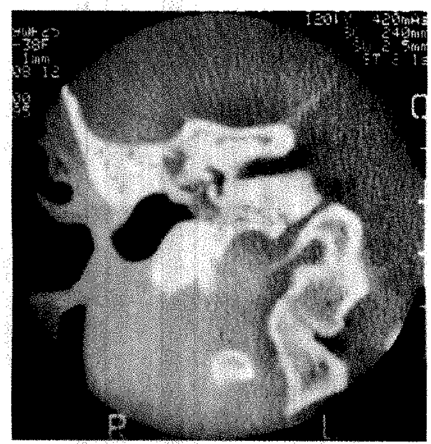

Fig 1.—Computed tomographic scan of right temporal bone obtained prior to angiography and embolization showing abnormal soft-tissue opacification in the middle ear cavity and mastoid air cells.

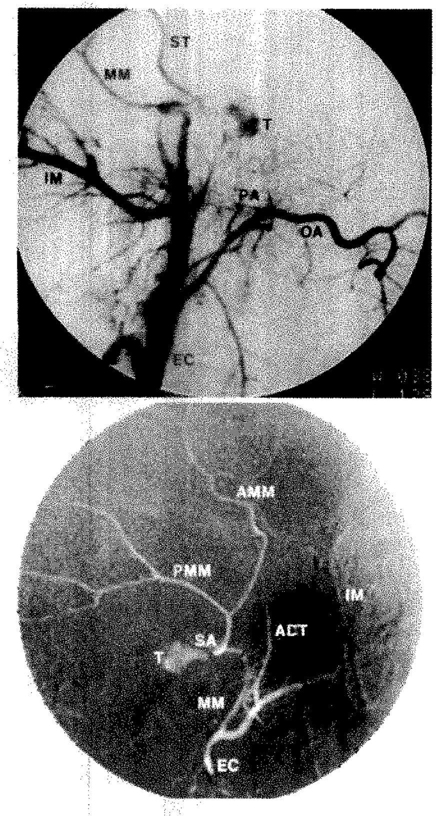

Fig 2.—Selective subtraction views of right carotid angiogram prior to embolization showing a vascular blush fed by a vessel originating from the middle meningeal artery (MM). Postembolization photographs (not shown) taken after selective embolization of the MM demonstrated complete absence of tumor blush. ST indicates superficial temporal artery; T, tumor; PA, posterior auricular artery; OA, occipital artery; EC, external carotid artery; IM, internal maxillary artery; AMM, anterior branch of MM; PMM, posterior branch of MM; ADT, anterior deep temporal artery; and SA, stapedial artery.

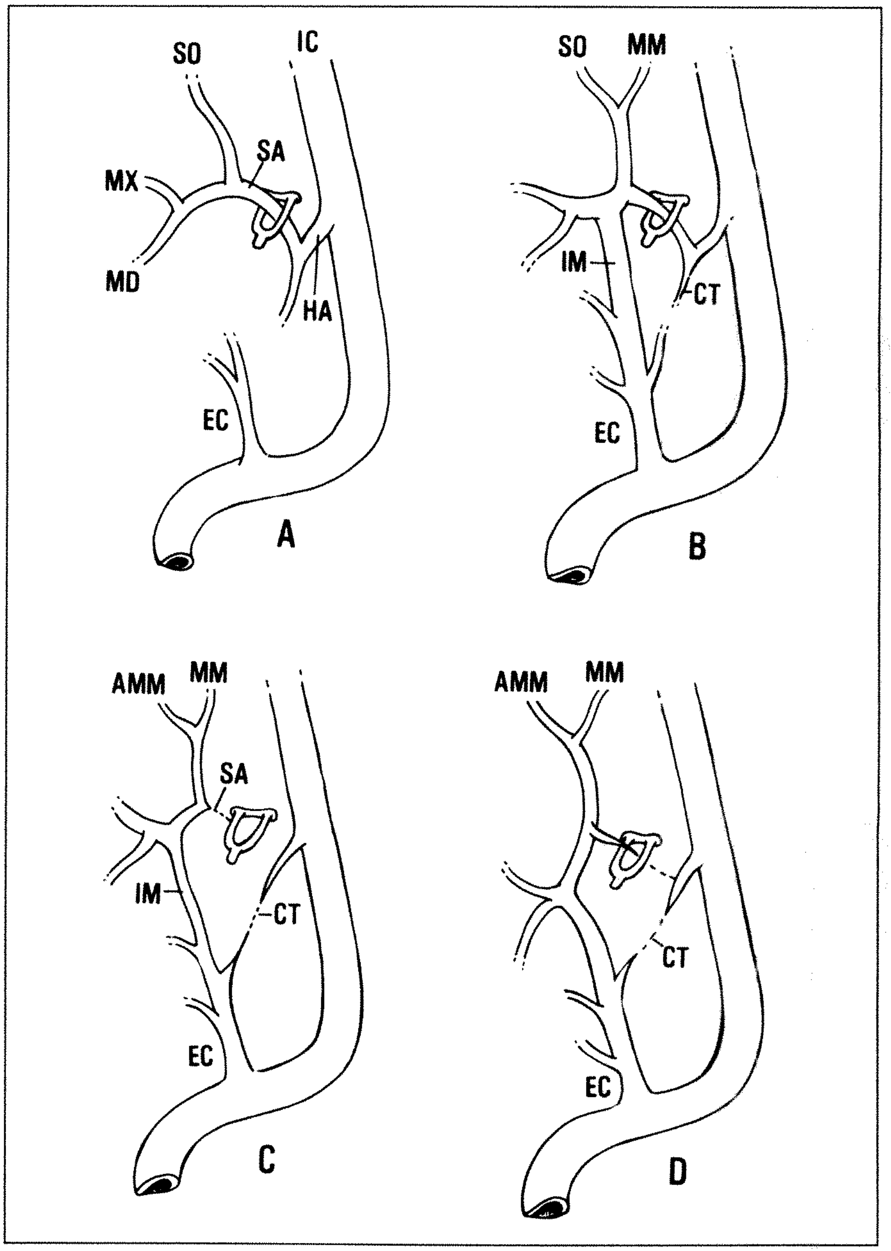

Fig 3.—Diagrams showing the embryological stages of the stapedial artery in man (from Lie[9]). A through C, Normal development. D, Persistent stapedial artery similar to that in the present case. SO indicates supraorbital branch; MX, maxillary branch; MD, mandibular branch; SA, stapedial artery; HA, hyoid artery; IC, internal carotid artery; EC, external carotid artery; IM, internal maxillary artery; MM, middle meningeal artery; CT, caroticotympanic branch; and AMM, anterior MM.

through a bony dehiscence. Distally it enters the cranial cavity and the middle cranial fossa, and divides into branches to the dura, where it terminates into the middle meningeal artery.[3]

A persistent stapedial artery can be associated with other middle ear anomalies, most commonly involving the stapes and facial nerve. Rarely, it may be associated with absence of an ipsilateral internal carotid artery. It may produce a conductive hearing deficit by occupying the entire stapedial obturator foramen, causing partial or complete fixation of the stapes.[4] It is postulated that a persistent stapedial artery could cause some types of tinnitus; however, to our knowledge, no cases have been documented.[5] The stapedial artery may be persistent in trisomy 13 and 15 syndromes,[6,7] along with other anomalies of the middle ear structures derived from the second branchial arch, including the stapes, the incudostapedial joint, and an abnormal course of a partially dehiscent facial nerve. A persistent stapedial artery has also been reported in isolated cases of Paget's disease, in otosclerosis, and in thalidomide deformities.

Padget[8] published a monumental article in 1948 based on graphic reconstruction of human embryos that clarified previous interpretations of the development of the cranial arteries. During development, the first and second embryonic arch arteries degenerate, probably before the third and more caudally placed arteries are fully formed. The dorsal segment of the second arch artery persists for a short time during fetal life as the stapedial artery. This artery passes through a mass of mesoderm that later chondrifies and ossifies as the stapes. The stapedial artery usually degenerates by the third month of fetal life. The third arch artery becomes the proximal part of the internal carotid artery.

At the height of its development, the stapedial artery has two major divisions (Fig 3). Immediately beyond the stapes, the dorsal division (supraorbital) passes cranially to the supraorbital region in company with the ophthalmic branch of the fifth nerve, and the ventral division (maxillomandibular) gives off two branches in association with the maxillary and mandibular roots of this nerve. Proximally, the hyoid artery originates from the internal carotid artery and forms the proximal stapedial stem, which involutes and is retained only as the caroticotympanic branch of the internal carotid artery. The ultimate area of involution and interruption of the stapedial artery occurs not at the carotid artery but at the stapes.

The supraorbital division undergoes anastomosis with the ophthalmic artery and is incorporated into the anterior branch of the middle meningeal artery as the stem of the supraorbital division involutes. This anterior middle meningeal artery branch may anastomose with the ophthalmic artery or, as a definite anomaly, give origin to the lacrimal and other orbital arteries.[8] In a similar manner, the external carotid artery, through its internal maxillary branch, undergoes anastomosis with the maxillomandibular division of the stapedial artery at its common trunk to form the first part of the middle meningeal artery. As discussed, the second part of the middle meningeal artery represents the proximal part of the supraorbital division of the stapedial artery. Following these developments, the stem of the stapedial artery is interrupted at the stapes just distal to the original hyoid artery, which remains as the small caroticotympanic branch of the internal carotid artery. The remnant of the stapedial stem is the superior tympanic branch of the middle meningeal artery.

CONCLUSIONS

To our knowledge, this is the first case report of a patient with a glomus tympanicum tumor vascularized by a persistent stapedial artery that was demonstrated angiographically and confirmed intraoperatively. The major vascular supply to the glomus tympanicum tumor in this case was via a small vessel originating from the anterior branch of the middle meningeal artery. This finding supports the presence of a persistent stapedial artery based on embryological review of the development of the cranial arteries[9]; however, it does not conclusively prove its existence. At the time of operation, a persistent stapedial artery was found coursing through the stapedial obturator foramen in a manner similar to that described by Steffen.[2]

Typically, the vascular supply to glomus tympanicum tumors arises from vessels overlying the promontory. In most cases bleeding is not a major problem during surgical removal, and it is not necessary to perform selective preoperative embolization of feeder vessels, thereby avoiding risks associated with embolization procedures. In this particular case, however, the major blood supply was the stapedial artery. Surgical control of bleeding at the level of the stapes and oval window is technically more difficult and associated with higher risk of injury to surrounding structures. Since angiography suggested the presence of a stapedial artery, we elected to perform selective arterial embolization preoperatively, with excellent results.

Vascular anomalies of the middle ear are rare. Among these, the mostly common known is the persistent stapedial artery. To better understand this anomaly, we have reviewed the embryological development of the stapedial artery and have discussed its clinical significance as well.

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Extramedullary Plasmacytoma of the Thyroid Associated With a Serum Monoclonal Gammopathy

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• Extramedullary plasmacytoma is a malignant plasma cell dyscrasia that is most commonly found in the head and neck. Progression to disseminated disease in the form of multiple myeloma occurs in 17% to 32% of cases. Herein, we describe a patient with extramedullary plasmacytoma of the thyroid gland in whom a serum monoclonal gammopathy resolved with surgery and irradiation of the primary. Although rare, this diagnosis should be considered in patients presenting with obstructive thyromegaly and autoimmune thyroiditis.

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Extramedullary plasmacytoma (EMP) is a rare soft-tissue plasma cell malignancy chiefly confined to the head and neck. While most of these lesions are isolated at the time of diagnosis, some are found in conjunction with multiple myeloma. Close meticulous follow-up is essential as 17% to 32% of patients will develop a disseminated plasma cell dyscrasia.[1] Plasmacytomas are most commonly a lesion of the nasal cavity, paranasal sinuses, and nasopharynx. Typically, they are found in older individuals, affecting men approximately four times as frequently as women. There have been 39 cases previously reported in the literature, where the primary lesion was found to be in the thyroid gland. We now describe a case of EMP in an immunocompetent woman arising in the thyroid associated with a serum monoclonal gammopathy as well as antithyroid antibodies.

REPORT OF A CASE

A 76-year-old white woman presented initially with a chief complaint of an enlarging neck mass. Thyromegaly was first noted approximately 1 year earlier and was treated with levothyroxine sodium (Synthroid, 0.125 mg/d). The medication was discontinued approximately 3 months prior to admission, with subsequent rapid enlargement of the thyroid gland. She presented to this hospital complaining of pressure in the neck and dyspnea on exertion.

Results of an examination, at the time of presentation, were significant for thyromegaly with her gland extending approximately from the anterior border of the trapezius muscle on one side to the anterior border of the contralateral trapezius (Fig 1). The mass was firm, nonmobile, and did not appear to be fixed to the skin.

Thyroid function studies were consistent with a hypofunctioning state thyroxine [T_4] = 3.2 mg% [5.2-10.9]; triiodothyromine [T_3] resin uptake, 0.63 (0.7 to 1.3); free thyroid index, 2.0 [5.2-10.9]; and thyroid stimulating hormone, > 50 IU/mL [< 8.0 IU/mL]. A computed tomographic scan revealed a large thyroid lesion associated with mediastinal adenopathy and bilateral neck adenopathy. The mass compressed the trachea circumferentially (Fig 2).

Treatment with levothyroxine sodium (0.125 mg/d) was continued, and the patient was taken to the operating room where she underwent a subtotal thyroidectomy. At the time of her surgery, the mass was adherent to, and wrapped around, the trachea. In addition, both recurrent laryngeal nerves were trapped within the tumor (Fig 3).

Two hundred grams of thyroid tissue were removed. Both lobes were encapsulated, lobulated, firm, and hemorrhagic. A cut section revealed tan tissue with focal areas of hemorrhage, fibrosis, and necrosis (Fig 4). Microscopic examination showed a diffuse replacement of nearly all thyroid tissue by mature, well-differentiated plasma cells with pyknotic nuclei or coarse chromatin clumping within the nucleus resulting in a "cartwheel" pattern (ie, heterochromatin aggregates adjacent to the nuclear membrane) (Fig 5).

Intravascular and extracapsular invasion was noted. The immunoperoxidase stains for immunoglobulins utilized both frozen and paraffin-embedded tissue. The majority of plasma cells stained positively

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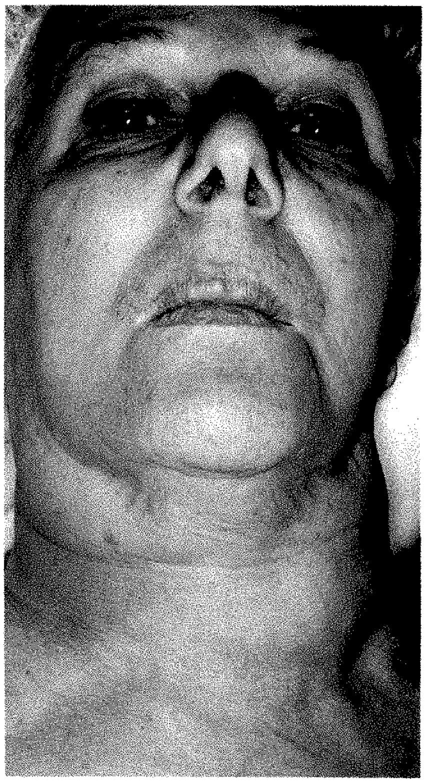

Fig 1.—Patient with thyromegaly and cervical adenopathy.

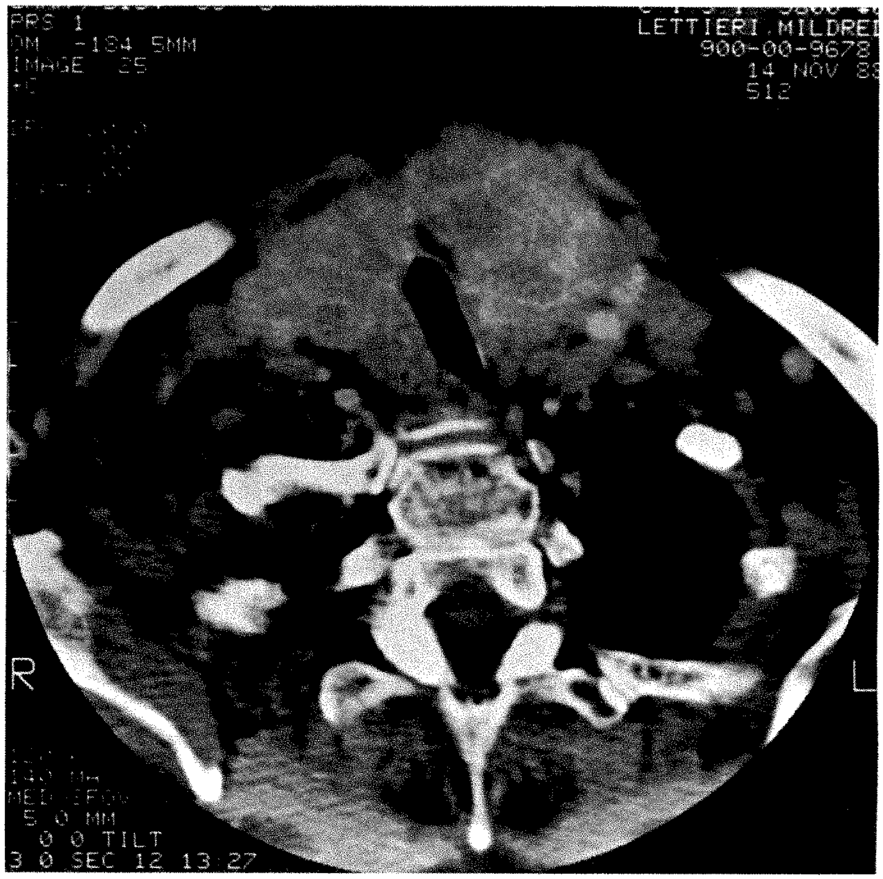

Fig 2.—Computed tomographic scan showing thyroid enlargement as well as regional adenopathy. Note tracheal compression.

for IgG and κ light chains (Fig 6); and were negative for IgA, IgM, and λ light chains.

Ultrastructurally, the plasma cells were round to oval, with abundant concentrically arranged lamellar rough endoplasmic reticulum and a prominent golgi apparatus (Fig 7). The eccentrically located nuclei demonstrated a cartwheel pattern (ie, heterochromatin aggregates adjacent to the nuclear membrane). Russell bodies (electron-dense structures that represent proteinaceous secretions by plasma cells) were noted within dilated cisternae of rough endoplasmic reticulum (Fig 8).

Her postoperative course was complicated by a temporary left true vocal cord paresis and persistent hypothyroidism (the patient was currently maintained on 0.15 mg of levothyroxine sodium a day). Serum protein electrophoresis revealed an IgG monoclonal gammopathy (2.13 g/dL). Urine protein electrophoresis was consistent with a possible paraprotein in the gamma region. Bone marrow biopsy and aspirate were within normal limits (plasma cells comprising <2% of the specimen). A skeletal survey revealed no osseous lesions. Antithyroglobulin and antimicrosomal antibodies were elevated at titers of 102-, 400-, and 400-fold, respectively. She subsequently was treated with external beam irradiation (50 Gy) to the neck and upper mediastinum. Quantitative immunoglobulins 3 months postoperatively showed an IgG level of 1490 mg/dL (normal, 1105 ± 236 mg/dL). Serum protein electrophoresis showed a gamma globulin fraction of 1.38 g/dL. Examination 20 months postoperatively revealed no evidence of disease.

COMMENT

Plasma cell lesions of the head and neck include plasma cell granuloma, multiple myeloma, EMP, and solitary plasmacytoma of bone. While plasma cell granuloma is thought to be inflammatory in origin, the remaining lesions are neoplastic. A useful scheme has been proposed to understand the plasmacytic dyscrasias as manifestations of a spectrum of disease.[2] Specifically, all are united by a single patho-

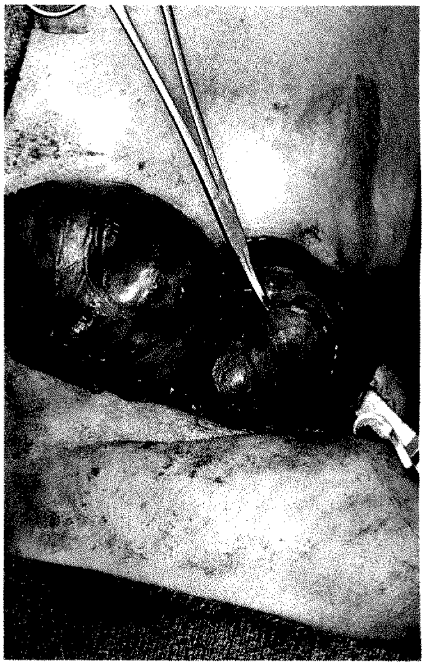

Fig 3.—Enlarged thyroid tissue. The hemostat identifies the recurrent laryngeal nerve.

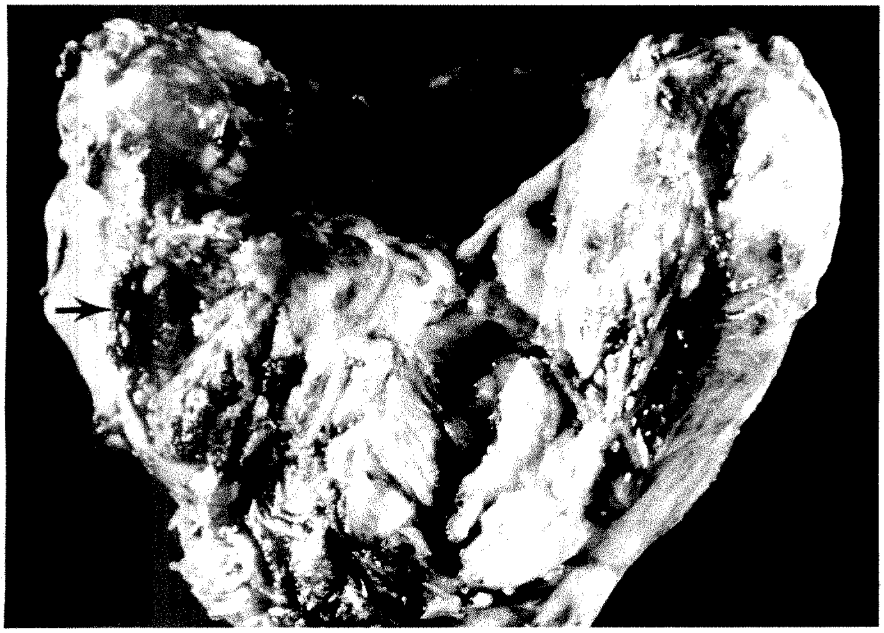

Fig 4.—Left thyroid lobe demonstrating encapsulated surface and central cut surface showing lobulated tan tissue with focal hemorrhage (arrow).

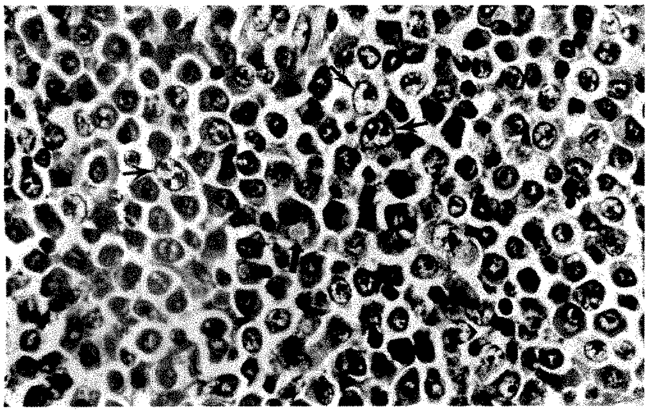

Fig 5.—Histologic section showing thyroid tissue totally replaced by many mature plasma cells with a "cartwheel" chromatin pattern. Occasional immature plasma cells with a fine chromatin pattern, distinctive nuclei, and a high nuclear to cytoplasmic ratio are pictured (thin arrows). A paranuclear hof is shown at center (thick arrow) (hematoxylin-eosin, x160).

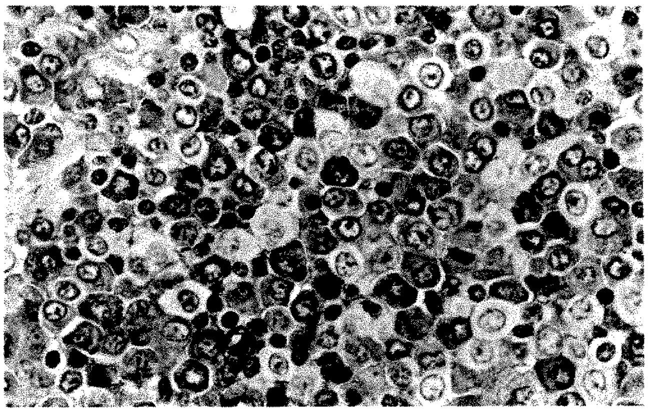

Fig 6.—Immunoperoxidase stain for κ light chain showing dark cytoplasmic staining, including most of the plasma cells (paraffin section; avidin-biotin complex method, x160).

Fig 7.—Electron micrograph demonstrating a mature plasma cell with an eccentrically located nucleus and a cartwheel chromatin pattern, abundant concentrically arranged rough endoplasmic reticulum (arrow), and a prominent Golgi apparatus (arrowheads) (uranyl acetate-lead citrate, x15 300).

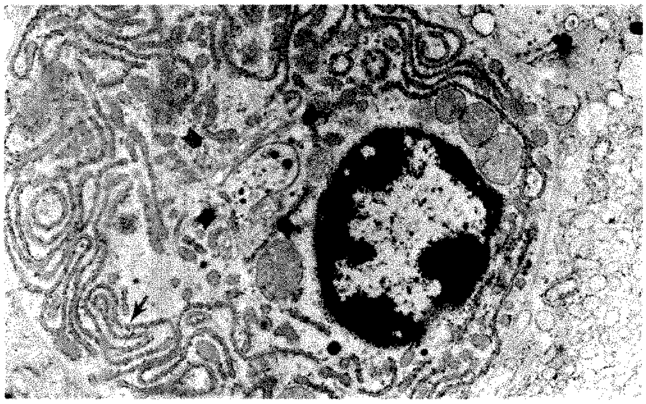

Fig 8.—Electron micrograph demonstrating plasma cells with numerous electron-dense round Russell bodies (arrows) located within dilated cisternae of rough endoplasmic reticulum (uranyl acetate-lead citrate, x 12 000).

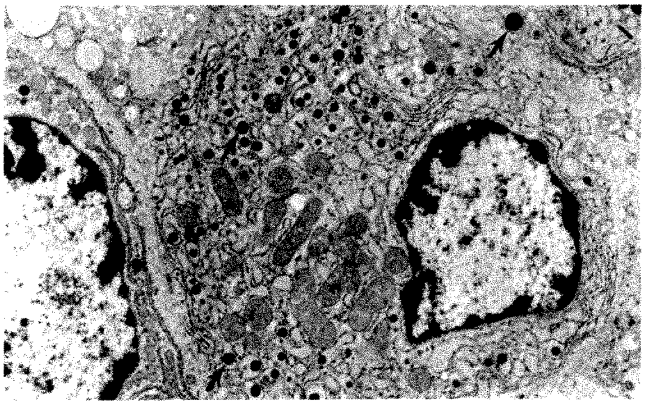

Table 1.—Correlation of Treatment of Extramedullary Plasmacytoma of the Head and Neck With Outcome*

		No. (%)		
Treatment	**No. of Patients**	**NED**	**DOD**	**Recurrence**
Radiation	126	70 (55)	35 (28)	21 (17)
Surgery	54	29 (54)	11 (20)	14 (26)
Radiation and surgery	39	15 (38.5)	15 (38.5)	4 (23)

*Based on analysis of data on 219 patients in 14 series. NED indicates no evidence of disease; DOD, dead of disease.

Table 2.—Clinical Features of Extramedullary Plasmacytoma of the Thyroid*

Parameter Measured	Reported Findings
Sex	
Male	49% (21/43)
Female	51% (22/43)
Age (range), y	37-82 . . .
Mean, y	58.5 . . .
Cervical	
Regional adenopathy	43% (9/21)
Serum M protein	33.3% (10/30)
Urine paraprotein	11% (2/18)
Antithyroid antibodies	63% (24/38)
Scintigraphy (thyroid)	
Hot	18% (2/11)
Cold	82% (9/11)
Thyroid functions	
Normal	53% (9/17)
Hypothyroid	47% (8/17)
Extrathyroid extension	50% (7/14)
Bone marrow	
Plasma cells	0% (0/23)
Normal	100% (23/23)
Primary treatment	
Surgery alone	40% . . .
Surgery plus radiation therapy	44% . . .
Surgery plus radiation therapy plus chemotherapy	14% . . .
Iodine 131 plus radiation therapy	2% . . .
Outcome	
Reccurrence	12% (6/43)
Multiple myeloma	
DOD	5% (2/41)
DIC	12% (5/41)
NED	73% (30/41)

*Numbers in parentheses indicate summary data of cases in the literature. DOD indicates dead of disease; DIC, dead of intercurrent disease; and NED, no evidence of disease.

logic change; ie, an abnormal proliferation of plasma cells derived from progenitor cells in or outside the bone marrow.

Extramedullary plasmacytoma is a plasma cell neoplasm of soft tissues found primarily in the head and neck, most commonly in the upper respiratory passages. Ninety-five percent of those afflicted are greater than 40 years old, with a peak age incidence in the seventh decade. It is roughly three to four times more common among men. Symptoms are typically related to the site of the lesion and in decreasing order of frequency are: a soft-tissue mass or swelling (80%), airway obstruction (35%), epistaxis (35%), tumor-associated local pain (20%), proptosis (15%), nasal discharge (10%), regional adenopathy (10%), and cranial nerve palsy (10%).[3] Only 10% involve multiple soft-tissue sites at diagnosis.

The work-up should focus on identifying other lesions and establishing the presence or absence of systemic disease, ie, multiple myeloma. Routine tests include complete blood cell count, bone marrow biopsy, serum protein electrophoresis, urine protein electrophoresis, and a skeletal survey. Prognostic features are debated and include the extent of the primary tumor, regional lymphadenopathy, local bone destruction, and persistence following initial treatment (with either irradiation or surgery). Survival is not thought to be related to the histopathologic findings of the primary lesion.

Local persistence/recurrence is a feature in approximately 10% to 15% of cases, and is associated with minimal morbidity. Death is nearly always from systemic spread and occurs in approximately 35% to 50%, usually within 2 years, with a 31% to 75% 5-year survival.[3]

Treatment has consisted of irradiation, surgery, or both. Reviewing available data on 219 patients in 14 published series, no single modality emerged as being preferable (Table 1). There was no significant difference between irradiation and surgery as the primary treatment modality. The increased mortality in those patients treated with both irradiation and surgery most likely reflects their increased tumor burden compared with those patients treated with a single modality.

Extramedullary plasmacytoma of the thyroid gland has a number of distinguishing features. Reviewing the 39 previously reported cases (in addition to our patient), the following features emerge (Table 2).[3-32] There is no gender preference with the disease afflicting men and women equally. The ages of the patients range from 37 to 82 years, with a mean of 58.5 years. Regional lymph nodes were involved in 43% of the cases, with no impact on prognosis. A serum monoclonal protein was detected in 33% (most commonly, IgG) at diagnosis; most resolving a few months after treatment of the primary lesion. A paraprotein was detected in the urine of 11% of those tested. Thyroid scintigraphy revealed a cold nodule of the gland in 9 (82%) of the 11 cases where it was obtained. Thyroid function studies were available in 17 patients; roughly half of whom were euthyroid and the remainder hypothyroid at the time of initial presentation. A bone marrow biopsy/aspirate was normal in all 23 patients where it was performed (plasma cells, <10%).

Concurrent chronic lymphocytic thyroiditis (Hashimoto's disease) was detected in 63% of the cases suggesting an autoimmune association for extramedullary plasmacytoma confined to the thyroid gland. This relationship with lymphocytic thyroiditis has also been noted in primary thyroid lymphoma.[33,34]

Nearly all of the patients (98%) were treated with some form of surgery (either total thyroidectomy, subtotal thyroidectomy, or hemithyroidectomy). Forty percent underwent surgery alone, 44% surgery plus irradiation, 14% surgery with both irradiation and chemotherapy, and one patient was treated primarily with iodine 131 plus irradiation. No significant difference was found between the form of initial therapy and outcome. Six patients experienced a local recurrence that was successfully managed in four patients with irradiation. Multiple myeloma was the cause of death in two patients. In an additional two cases, multiple myeloma was implicated although not proven due to lack of data. Follow-up ranged from 1 to 120 months, with a mean of 34 months. The two patients who developed multiple myeloma did so 4 years after the initial appearance of EMP. It is, therefore, possible that longer follow-up might lead to the discovery of a higher incidence of subsequent systemic dissemination. We suggest, therefore, that patients with EMP of the thyroid be followed up indefinitely. Furthermore, although rare, this diagnosis should be considered in the patient presenting with obstructive thyromegaly associated with autoimmune thyroiditis.

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Resident's Page

ROBERT E. FECHNER, MD, SECTION EDITOR

University of Virginia School of Medicine, Charlottesville

PATHOLOGIC QUIZ CASE

Thomas M. Andrews, MD, Charles M. Myers III, MD, Cincinnati, Ohio

An 11-year-old girl presented with a history of a previous admission for *Streptococcus pneumoniae* bacteremia presumably secondary to a right-sided pansinusitis (Fig 1). A computed tomographic scan demonstrated a bony mass in the right ethmoidal sinus expanding into the maxillary sinus and impinging on the lamina papyracea without evidence of destruction (Fig 2). Examination at the initial evaluation revealed an intercanthal distance of 38 mm, a mild headache, and proptosis of the right eye.

A bone scan demonstrated increased uptake in the medial aspect of the right orbit and ethmoidal sinus, consistent with an osteoclastic lesion.

The patient was taken to the operating room, where a lateral rhinotomy and an external ethmoidectomy revealed a blue-gray mass, which was completely excised. Figure 3 is a representative photomicrograph of the lesion.

What is your diagnosis?

PATHOLOGIC QUIZ CASE 2

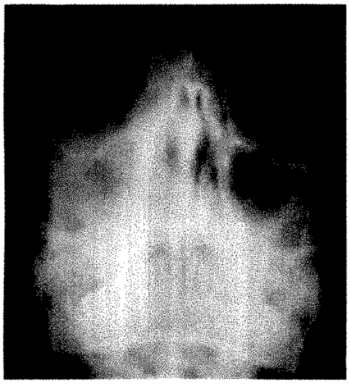
Diane Radkowski, MD, Gerard Domanowski, MD, Boston, Mass

A 42-year-old married man without a significant medical history initially presented to the otolaryngology clinic complaining of a 3-month history of a progressively enlarging right facial mass. He also described progressive right aural fullness. There was no history of trauma, and the patient denied fever, chills, or other constitutional symptoms.

On physical examination, the patient was observed to be a healthy-appearing white man. A 3 × 3-cm nontender, firm mass was noted in the preauricular area on the right side. A smaller 2 × 2-cm mass was noted in the tail of the parotid gland on the same side. An asymptomatic 2 × 2-cm mass was also noted in the tail of the parotid gland on the opposite side. The right external auditory canal was partially obstructed secondary to extrinsic compression by the preauricular mass, and trismus was noted to 3 cm. The patient was also found to have multiple small, bilateral cervical nodes measuring less than 1 × 1 cm. A contrast computed tomographic scan was obtained (Fig 1), and the patient was taken to the operating room.

What is your diagnosis?

PATHOLOGIC QUIZ CASE 1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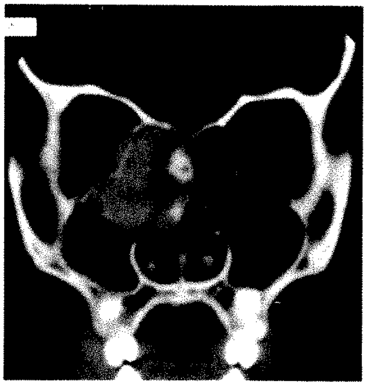
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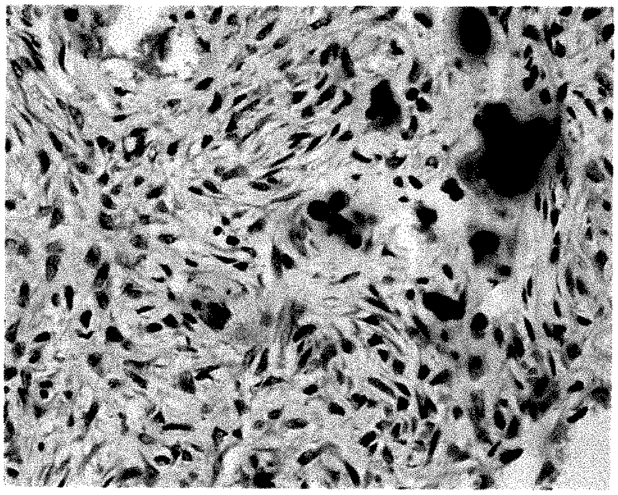
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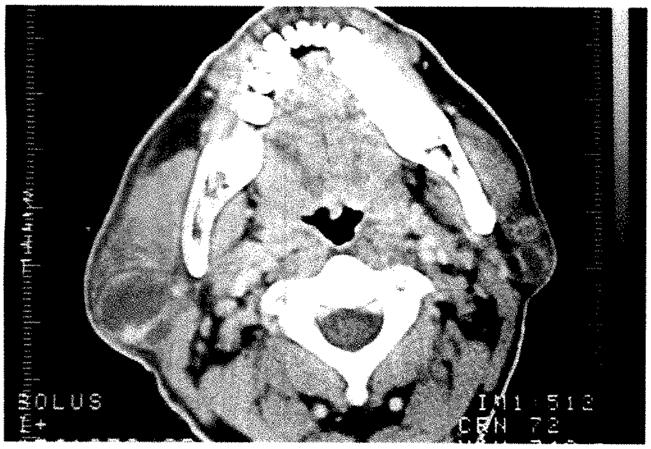
PATHOLOGIC QUIZ CASE 2



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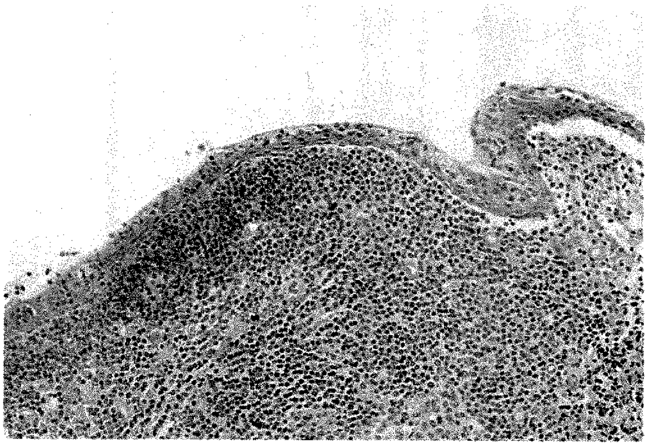
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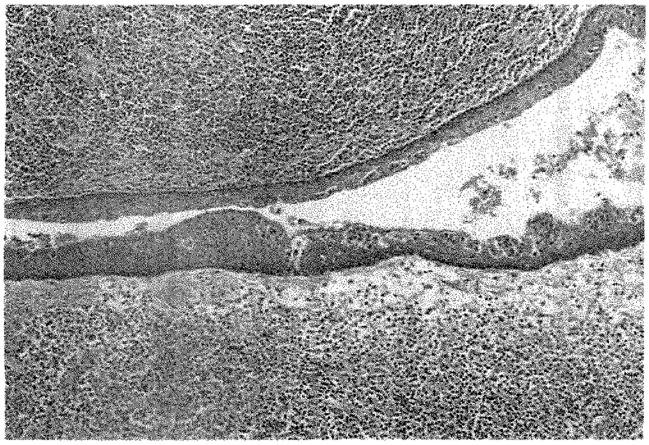

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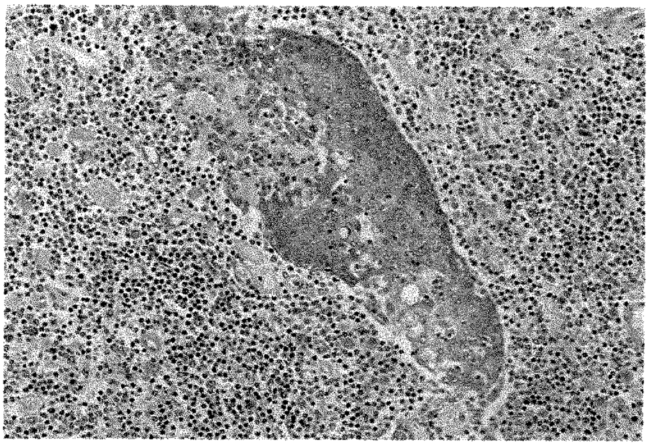

Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 1

Pathologic Diagnosis: Transitional (psammomatous) meningioma of the ethmoidal sinus.

Primary ectopic meningiomas are rare. Thirty cases of ectopic paranasal sinus meningiomas have been reported in the literature: 9 in the ethmoidal sinus, 8 in the frontal sinus, 6 in the maxillary sinus, 2 in the sphenoidal sinus, and 5 in more than one sinus. The most common site of ectopic meningioma is the orbit and optic nerve.[1]

Common clinical features include nasal obstruction, exophthalmos, and epistaxis. Females are predominantly affected. Forty-three percent of patients are younger than 20 years, with a mean age at diagnosis of 31 years. Radiographically, meningiomas demonstrate sclerosis or hyperostosis of neighboring bone, bony destruction, abnormal vascularity, and tumor calcification.[1,2]

The pathogenesis of meningiomas is uncertain, although several theories have been presented. They are thought to be derived from cap cells of arachnoid villi. Ectopic meningiomas may be due to pinched-off embryonal arachnoid rests,[3] derived from ectopic pacchionian bodies,[4] or arise from multipotential mesenchymal cells.[5] Clinical evidence supports pathogenesis from arachnoid rests left behind near developmental lines of fusion.

Russel and Rubinstein[6] outlined four major variants: (1) *syncytial meningiomas* (10%), which demonstrate sheets of polygonal cells; (2) *transitional meningiomas* (75%), with variable numbers of psammoma bodies and a whorling pattern (also known as psammomatous meningiomas); (3) *fibroblastic meningiomas* (10%), demonstrating bands of collagen and generally less cellularity; and (4) *angioblastic meningiomas* (5%), which are very cellular with a rich vascular stroma.

Surgical excision is the treatment of choice. Usual paranasal sinus approaches may have to be combined with intracranial techniques to achieve total tumor extirpation. A transbasal approach has recently been described.[1]

Meningiomas usually exhibit benign behavior. However, they do occasionally invade adjacent bone and fibrous tissue and may act in a more malignant fashion with rare metastases. Ho,[7] however, reports that patients with meningiomas of the paranasal sinuses usually have a good prognosis.

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Clinical and Pathologic Diagnosis

PATHOLOGIC QUIZ CASE 2

Pathologic Diagnosis: Acquired immunodeficiency syndrome–related parotid lymphadenopathy.

Persistent generalized lymphadenopathy is a well-documented and accepted companion to human immunodeficiency virus (HIV) seropositivity and often precedes the development of acquired immunodeficiency syndrome (AIDS)-related opportunistic infections and neoplasms. Salivary glands are now appearing as possible initial foci of these lymphadenopathies in the HIV-positive patient.[1]

Normally, salivary glands are associated with 5 to 10 lymph nodes. In the parotid gland, these lymph nodes lie within the parotid capsule. Embryologically, this anatomic association arises because of the relatively late development of the parotid capsule. The lymphoid tissue therefore becomes incorporated into the gland. In contrast, the capsules of the submandibular and sublingual glands develop at an earlier stage, and the associated lymph nodes are found outside the glands. As with lymphoid tissue elsewhere in the body, these nodes become possible primary targets for opportunistic, viral, and neoplastic AIDS-related processes.

Clinically, the enlarged salivary glands are painless, and the patient is often without other manifestations of the AIDS-related complex. Follow-up of these patients, however, invariably reveals the subsequent development of a more "full-blown" AIDS picture. Despite surgical resection, the salivary gland lymphadenopathy often recurs.[2]

Histologically, the parotid gland lesion of AIDS demonstrates enlarged intraparotid lymph nodes with follicular hyperplasia, dilated ducts, and sloughing of keratin debris with loose squamous cells in the lumen (Fig 2).[1,2] In some regions, the proliferation of the squamous duct lining will actually obliterate the entire lumen. In other areas, there is a cystic dilatation of the ducts now lined with stratified squamous epithelium. The walls of these cysts contain a rich lymphohistiocytic infiltrate (Fig 3).[3]

Regions of squamous epithelium surrounded by lymphocytes are occasionally found. These areas of squamous metaplasia presumably of ductal origin contain eosinophilic material and resemble the benign epimyoepithelial lesion seen in Sjögren's syndrome (Fig 4). The epithelial islands in the latter, however, are derived from basal myoepithelium and are not ductal in origin.[4]

Of particular importance is the risk of non-Hodgkin's lymphoma developing in the salivary gland lymphoid tissue. Of all primary extranodal malignant lymphomas, 5% develop in the intraparotid lymph nodes.[1] In the patient with AIDS, these lymphomas may represent malignant transformation of the benign lymphepithelial cysts more commonly encountered.[2] The malignant lymphomas of the parotid gland and the other salivary glands exhibit the same histologic and clinical characteristics as those arising elsewhere.

Interest in a noninvasive means of identifying these AIDS-related benign lymphoepithelial cysts has prompted closer evaluation of specific radiographic findings. Computed tomographic scans were obtained on asymptomatic high-risk patients at New York (NY) Hospital with clinically evident parotid lesions. The scan revealed multiple intraparotid masses in more than 80% of the patients scanned. Of these, 75% showed bilateral involvement despite a clinical assessment of unilateral, solitary masses in all but approximately 10% of the patients examined. The parotid masses had a homogeneous, cystic appearance with a well-circumscribed minimally enhancing rim. The cysts were predominantly in the superficial portion of the gland. While the etiology of the cysts is not clear, their multiplicity and bilaterality make them unique in the possible diagnostic options for parotid cystic lesions (such as retention cysts, first branchial cleft cysts, or benign lymphoepithelial cysts not associated with AIDS). While these lesions appear to most closely resemble Warthin's tumors, the presence of cervical adenopathy in 18 of 18 patients studied excludes this diagnosis.[3]

Patients presenting to the otolaryngologist with an asymptomatic parotid mass who are HIV positive or in a high-risk group should uniformly be evaluated with a computed tomographic scan prior to any surgical procedure. If radiographic studies revealed multiple, bilateral cystic lesions with diffuse cervical adenopathy, surgery may be avoided. In the face of a near pathognomonic radiographic finding, tissue diagnosis is not imperative, and the possible risks of surgery may be avoided.

The patient subsequently stated that he lived a bisexual life-style, and he tested positive for HIV following review of his operative pathologic findings.

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Residents and fellows in otolaryngology are invited to submit quiz cases for this section and to write letters to the ARCHIVES *commenting on cases presented. Quiz cases should follow the patterns established and must be submitted in duplicate. Photomicrographs must be clear and can include an outline drawing with important structures labeled, especially in the case of histopathology of the ear. Illustrations must be submitted as positive color transparencies (35 mm preferred). Do not submit color prints unless accompanied by original transparencies. Transparencies should be carefully packaged in a separate container. Please do not submit glass-mounted transparencies or the actual glass histology slides. Material for the Resident's Page should be mailed to the Chief Editor.*

Reprints not available.

Letters to the Editor

Iatrogenic Retropharyngeal Emphysema

To the Editor.—I am writing this letter concerning the article by Breznick and Saporito[1] on "Iatrogenic Retropharyngeal Emphysema With Impending Airway Obstruction." There is a very simple method of eliminating air in tissue.

Of course, air is 80% nitrogen. Nitrogen is inert. Oxygen is picked up by the bloodstream very rapidly, and the nitrogen remains a problem. Nature abhors spaces and will then begin to fill those spaces with tissue fluids that can become infected quite rapidly. Although nitrogen is inert, it can be eliminated fairly rapidly. This treatment was not mentioned under the "Management Aspects" section of the article.

Because nitrogen is inert, the only way to eliminate nitrogen is to create as large a partial pressure difference between the nitrogen in the tissue and the nitrogen in the blood. Then, according to the general gas laws, the nitrogen gas will flow to the area of lower concentration.

Management requires the washing of the nitrogen out of the blood. This means that the patient has to be kept in a tent of oxygen of as high a percentage as possible to create that great partial pressure difference. On day eight the patient discussed in the article underwent a computed tomographic scan that showed emphysema. Usually it washes out overnight if high oxygen levels can be maintained.

This is an interesting treatment. It has an interesting theoretic rationale, and does work on a practical basis.

Yale J. Berry, MD
Boston, Mass

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1. Breznick DA, Saporito JL. Iatrogenic retropharyngeal emphysema with impending airway obstruction. *Arch Otolaryngol Head Neck Surg.* 1989;115:1367-1372.

In Reply—Dr Berry's consideration is supported physiologically. Air cavities within the body tend to decrease in size and ultimately disappear. During air breathing, the transfer of gases from a high partial pressure within cavities to a lower partial pressure in the blood forms the basis for the resorption of air spaces such as subcutaneous emphysema.[1] Breathing 100% oxygen reduces the partial pressure of nitrogen in the blood, thereby increasing the gradient for the resorption of nitrogen from body cavities.[2]

This method of conservative management is appropriate for the majority of cases of uncomplicated interstitial emphysema. Our patient's ominous clinical situation necessitated rapid surgical intervention. In retrospect, the postoperative resolution of his interstitial emphysema may have been accelerated by this nitrogen washout technique. However, it was an allergic reaction to intravenous penicillin that resulted in his prolonged hospitalization.

David A. Breznick, MD
John L. Saporito, MD
Long Branch, NJ

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1. Munson ES. Transfer of nitrous oxide into body air cavities. *Br J Anaesth.* 1974;46:202-209.
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News and Comment

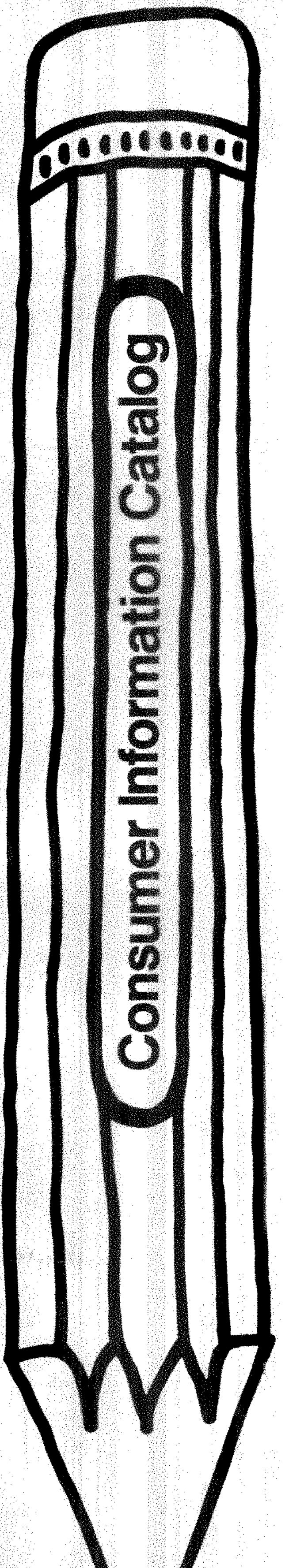
Head and Neck Surgery 1990.—Dartmouth-Hitchcock Medical Center, Section of Otolaryngology/Audiology, will present a program on recent advances in head and neck surgery, featuring a national faculty. The program will be held October 4 through 6, 1990, in the Hanover Inn at Dartmouth College, Hanover, NH. Adequate time will be allowed for discussion and relaxation in addition to lecture sections. For further information, contact Karen Griswold, Planning and Production Coordinator, Office of Continuing Education in the Health Sciences, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756; (603) 646-5744.

Harvard Medical School Announces Postgraduate Course.—From October 1 through 5, 1990, Harvard Medical School, Boston, Mass, will offer a postgraduate course on current concepts in neuroradiology, head and neck radiology, and the neurologic utility of magnetic resonance imaging. This course, which will be held at The Lafayette Hotel, Boston, will offer 40 hours of Category 1 credit. For further information, contact Department of Continuing Medical Education, Harvard Medical School, Boston, MA 023114.

American Auditory Society Announces Annual Meeting.—The 17th annual meeting of the American Auditory Society will be held on November 15, 1990, in Seattle, Wash. For further information, contact Robert A. Dobie, MD, Chair, American Auditory Society Program Committee, Otolaryngology-Head and Neck Surgery, University of Washington RL-30, Seattle, WA 98195.

Endoscopic Sinus Surgery.—The Office of Continuing Medical Education of the University of Michigan Medical School, Ann Arbor, is sponsoring an upcoming conference entitled "Endoscopic Sinus Surgery." This course, which will be held on August 17 and 18, 1990, at the Towsley Center, University of Michigan, Ann Arbor, is presented by faculty from the University of Michigan and The Johns Hopkins University, Baltimore, Md, and is designed to give the participant both theoretical and practical knowledge concerning endoscopic sinus surgery. Fifteen hours of Category 1 credit will be offered. For further information, contact the Registrar, Office of Continuing Medical Education, G-1100 Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.

Pan American Congress of Otorhinolaryngology-Head and Neck Surgery Announced.—The 22nd Congress of the Pan American Association of Otorhinolaryngology-Head and Neck Surgery will be held at the Sheraton Hotel in Buenos Aires, Argentina, from December 1 through 5, 1990. For further information, contact Dr Alejandro Terzian, Secretary General, Delfino Turismo SRL, San Martin 427 (1004), Buenos Aires, Argentina; 54 1 394-2014, -2247, or -4181; fax, 54 1 111595 or 54 1 3945379



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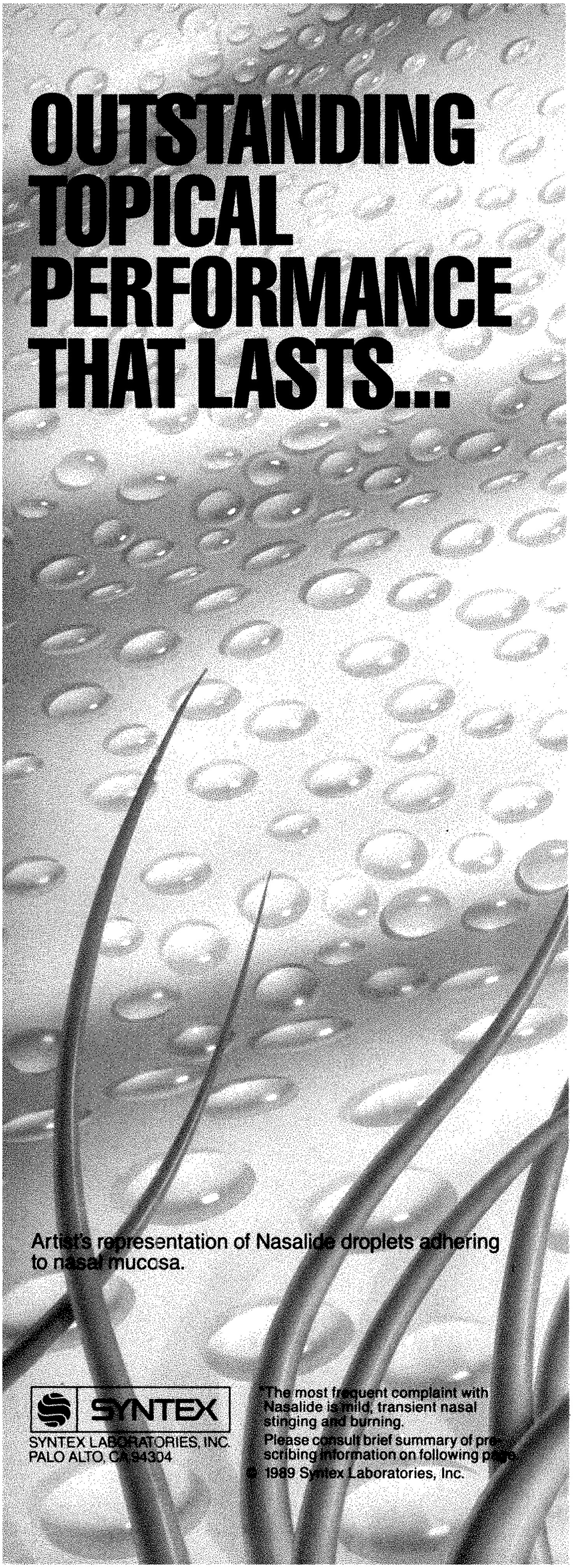

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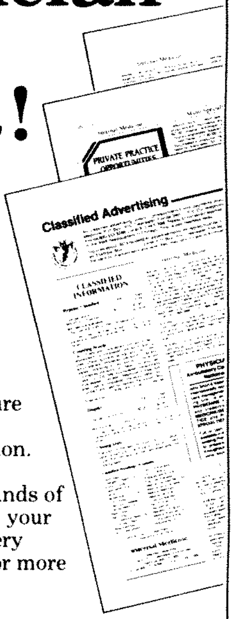

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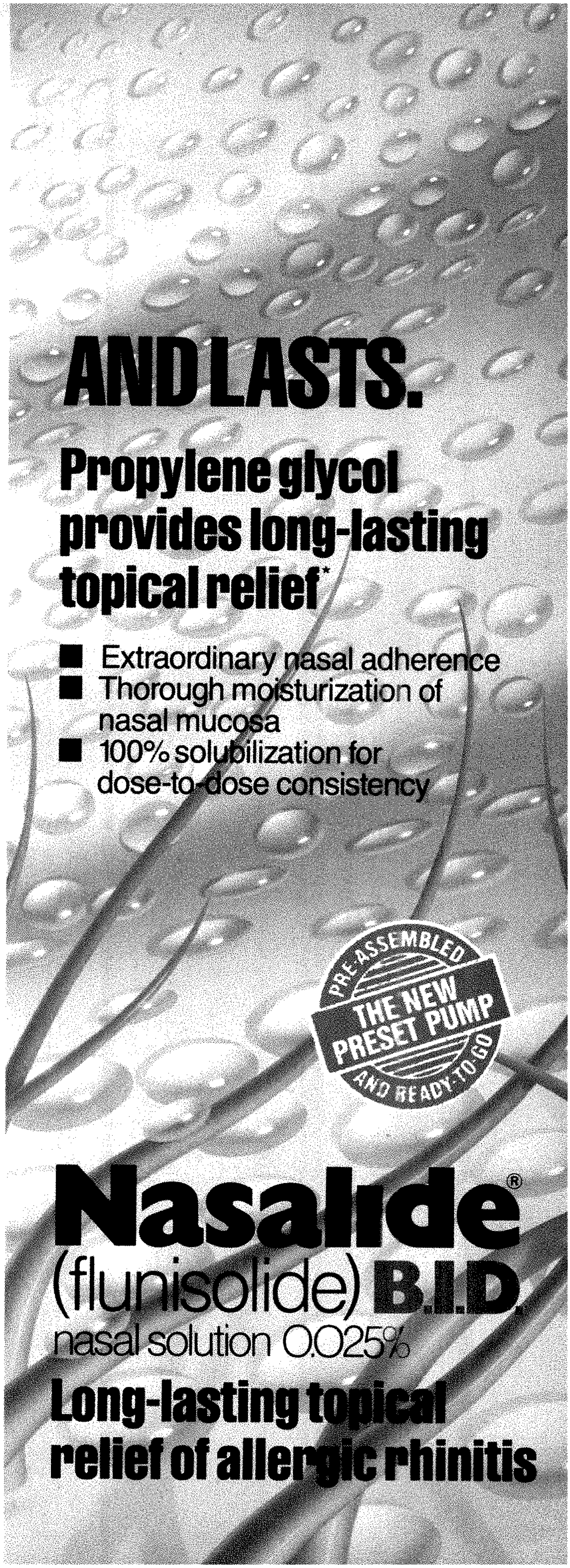
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Contraindications: Hypersensitivity to any ingredients

Warnings: Patients transferred from systemic steroid therapy to Nasalide should be monitored to avoid acute adrenal insufficiency in response to stress. Since some patients may experience symptoms of withdrawal, attention must be given to patients previously treated for prolonged periods with systemic corticosteroids, particularly those with associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of symptoms. Nasalide should be used with caution in patients on alternate-day prednisone for any disease.

Precautions: General: Localized *Candida albicans* infections of the nose and pharynx occurred only rarely in clinical studies, but if such an infection presents, treatment with appropriate local therapy or discontinuation of Nasalide treatment may be required

Flunisolide is absorbed into the circulation. Systemic effects have been minimal with recommended doses but larger doses should be avoided since excessive doses may suppress hypothalamic-pituitary-adrenal function

Nasalide should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

In patients who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery, or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Information for Patients: Nasalide should be used as directed at the prescribed dosage. Nasal vasoconstrictors or oral antihistamines may be needed until the effects of Nasalide are fully manifested. The patient should follow the Patient Instructions carefully and should contact a physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs

Carcinogenesis: Long-term studies showed a slight increase in the incidence of pulmonary adenomas in mice, but not in rats

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in low and mid-dose groups was comparable to controls.

Pregnancy: Pregnancy Category C. The drug has been shown to be teratogenic and fetotoxic in rabbits and rats. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because other corticosteroids are excreted in human milk, caution should be exercised when the drug is administered to nursing women

Adverse Reactions: The most frequent complaints were mild transient nasal burning and stinging (reported in approximately 45% of patients). These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of these symptoms.

Incidence of 5% or less: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headaches and loss of sense of smell and taste. As is the case with other nasally inhaled corticosteroids, nasal septal perforations have been observed in rare instances.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism could occur.

Dosage and Administration: Full therapeutic benefit requires regular use and is usually evident within a few days, but up to 3 weeks may be required for some patients to achieve maximum benefit. Patients should use a decongestant and clear their nasal passages of secretions prior to use. Recommended starting dose in adults: 2 sprays in each nostril b.i.d. If needed, increase to 2 sprays t.i.d

Recommended starting dose in children (6-14 years): 1 spray in each nostril t.i.d. or 2 sprays in each nostril b.i.d. Not recommended for use in children less than 6 years old

Total daily doses: not to exceed 8 sprays in each nostril for adults and 4 sprays in each nostril for children.

Maintenance dose: smallest amount necessary to control symptoms.

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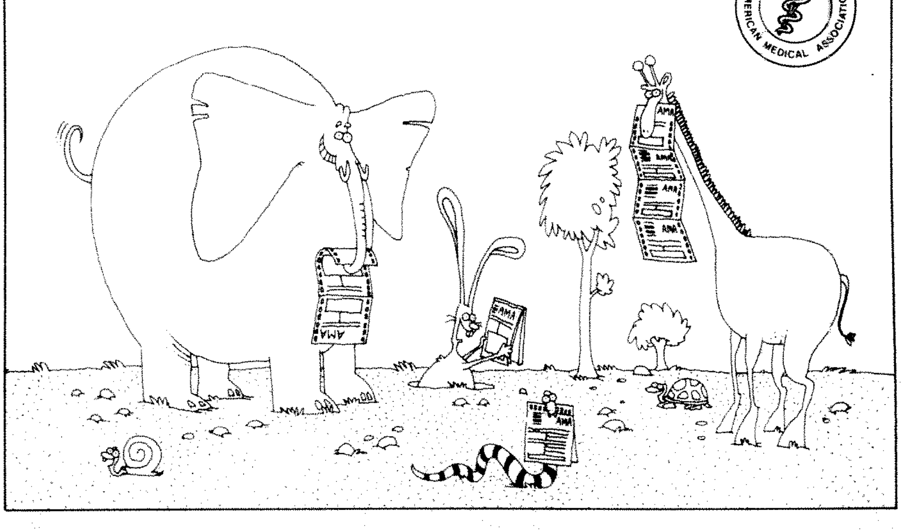

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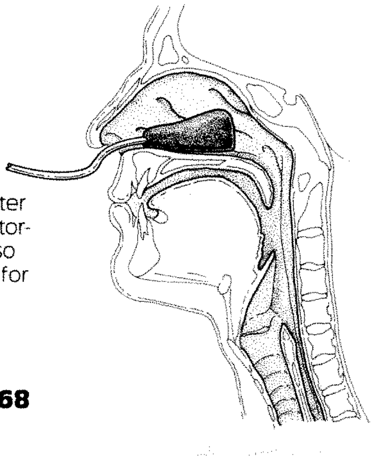

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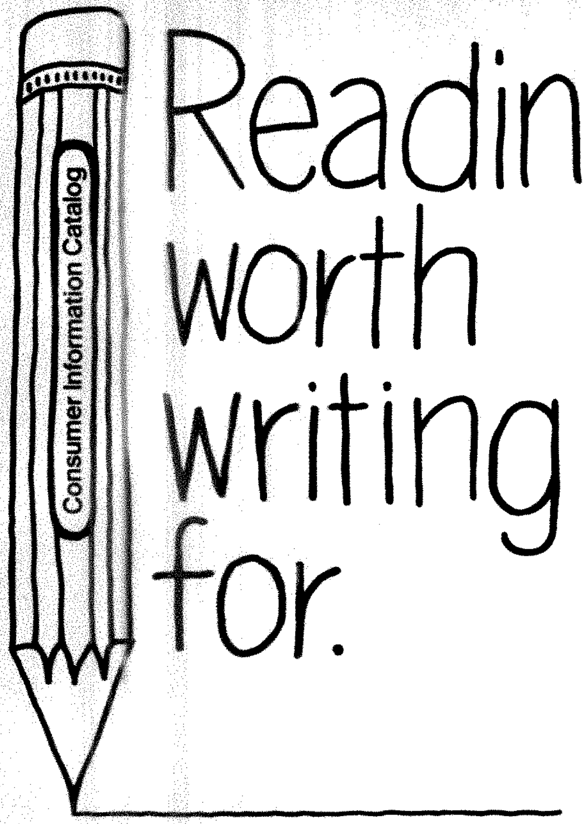

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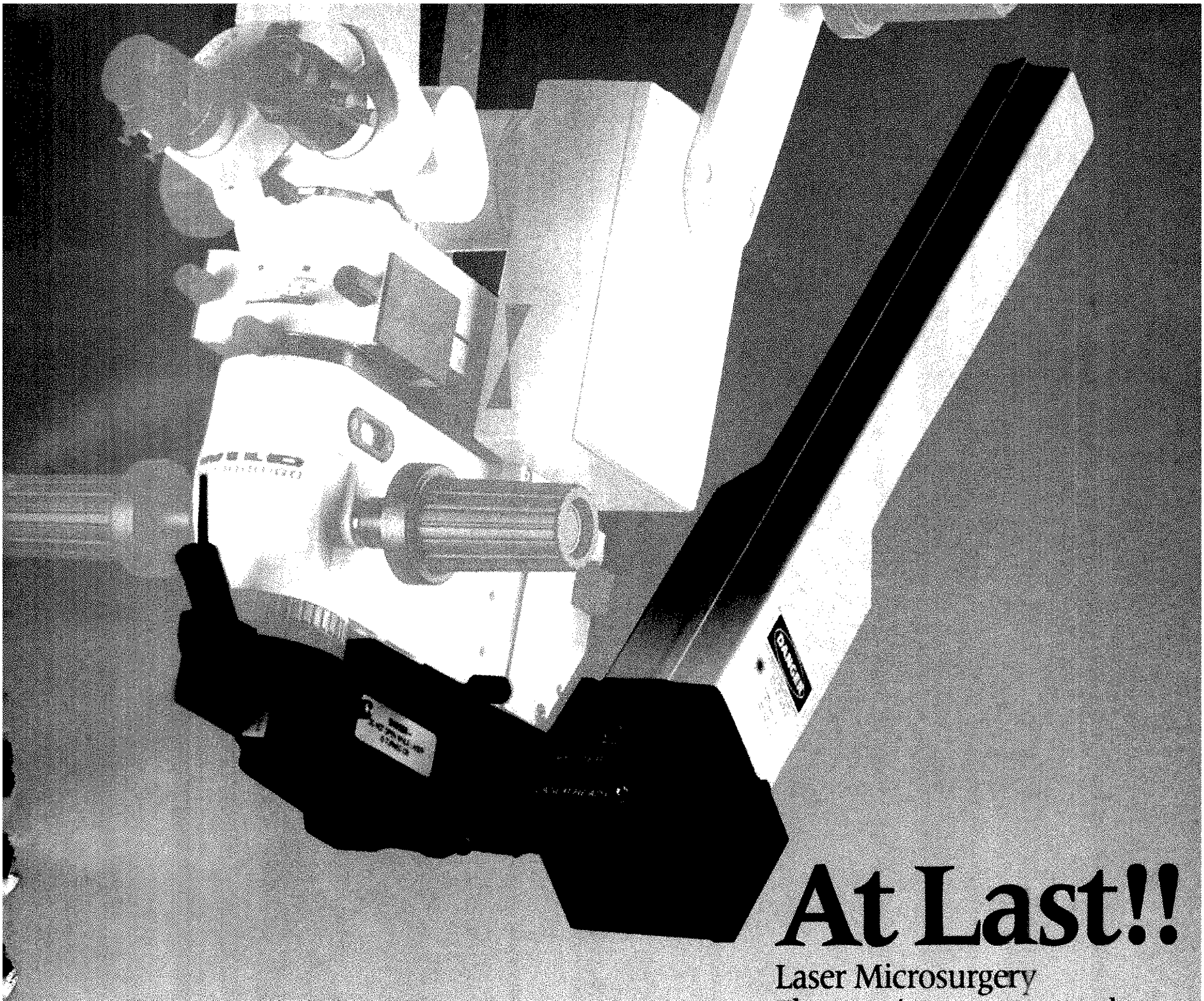

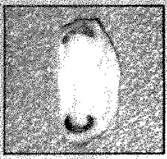

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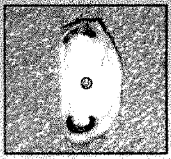

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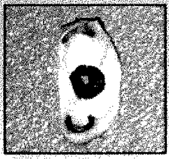

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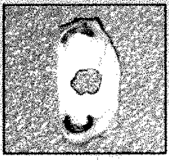

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PACIFIC NORTHWEST — Group Health Cooperative of Puget Sound, a 375,000-member prepaid group practice, currently has a position available for an otolaryngologist. Referral only practice in a multi-specialty organization. Wonderful practice opportunity located in the scenic Puget Sound area. To inquire, write to: Manager, Medical Staff Personnel, 521 Wall Street, Seattle, WA 98121.

LOCUM STAFF SURGEON positions in New Zealand. Applications are invited from suitably qualified applicants for the above. A flexible package is available with the timing, duration and sessional basis of the appointment being open to negotiation. The successful applicant must have a United Kingdom Fellowship in Otolaryngology or Australasian Fellowship in Otolaryngology. Wellington Area Health Board serves a population of about 400,000. The major component of the ENT service is based at Wellington Hospital — a teaching hospital linked to the University of Otago. Application forms and conditions of appointments are available from: Ruth Halford, Human Resources Unit, Wellington Area Health Board, P.O. Box 10 245, Wellington, New Zealand. Telephone: (04) 725 679. Facsimile: (4) 710 612. Closing date: open.

OTOLARYNGOLOGY — Brainerd, Minnesota. Join twenty MD, multi-specialty clinic. No capitation. No start-up costs. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/ write: Curtis Nielsen (218) 828-7105 or (218) 828-4901. P.O. Box 524, Brainerd, MN 56401.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AOTO, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

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OTOLARYNGOLOGY Consultants of Memphis - Expanding three doctor group seeks facial plastic, fellowship-trained associate to join a diverse, quality oriented and busy practice. Four fully staffed offices. Associated with the areas major medical centers. Competitive salary and comprehensive benefits. Opportunities leading to partnership after two years. Please direct inquiries and CV to: Thomas E. Long, MD; Rande H. Lazar, MD, 848 Adams, Suite 401, Memphis, TN 38103.

77 PHYSICIAN MULTI-SPECIALTY group seeks BC/BE ENT physician. Excellent fringe benefits. Full association possible within three years. This group is located in the far western suburbs of Chicago in an area offering excellent schools, housing and recreational facilities. Send CV to: Box #403, c/o AOTO.

VIRGINIA — Otolaryngology opportunities in high growth areas near Chesapeake Bay. Send vitae to: Janet Clayton, AM Care Physician Search, P.O. Box 2816, Durham, NC 27715. (800) 477-0600.

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Submit a CV and letters of reference to:

Thomas J. Balkany, MD
Professor and Vice-Chairman
Department of Otolaryngology (D-48)
UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
P.O. Box 016960, Miami, FL 33101

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Lakeview Medical Center

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We have complete audiology facilities and offices near two hospitals where most surgery is performed. This group is located in a St. Louis County community of approximately 350,000 which has outstanding living and working conditions.

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If this opportunity is of interest to you, please send your curriculum vitae to:

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Christian Hospital Northeast
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Otolaryngologist

BC/BE — Associate with well-established 31-MD multi-specialty group, located 45 miles from San Francisco and 20 minutes from Napa Valley in growing community serving 140,000. Patients include both fee-for-service and prepaid health plan.

Attractive compensation and benefits. Malpractice provided.

Send CV to:

Dominic Scolaro
Caller Box 4020
Fairfield, CA
94533-0410
(707) 426-3911

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Board-Certified or Board-Eligible

Three-physician group in north central Wisconsin seeking a personable, well-trained and qualified person to share in a progressive, well established practice.

This well equipped and staffed office is located in a modern, 300-bed hospital. The community and surrounding area has a population of 100,000 (+) and provides excellent educational, cultural and recreational opportunities.

Please send curriculum vitae to:

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David W. Kennedy, MD
Department of Otolaryngology-
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The Johns Hopkins Hospital
600 N. Wolfe St., Carnegie 434
Baltimore, Maryland 21205

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For a physician application, please call (800) 328-5278. If calling from outside of California, please call (800) 541-7945 or send your curriculum vitae to: Irwin P. Goldstein, M.D., Associate Medical Director, SCPMG, Dept. 016, Walnut Center, Pasadena, CA 91188-8013.

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Otolaryngologists

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Cary Ear, Nose & Throat Clinic
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Cary, North Carolina 27511

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For additional information, contact:
Robin L. Wagner, Administrative Coordinator
(412) 647-2227 or FAX (412) 647-7964

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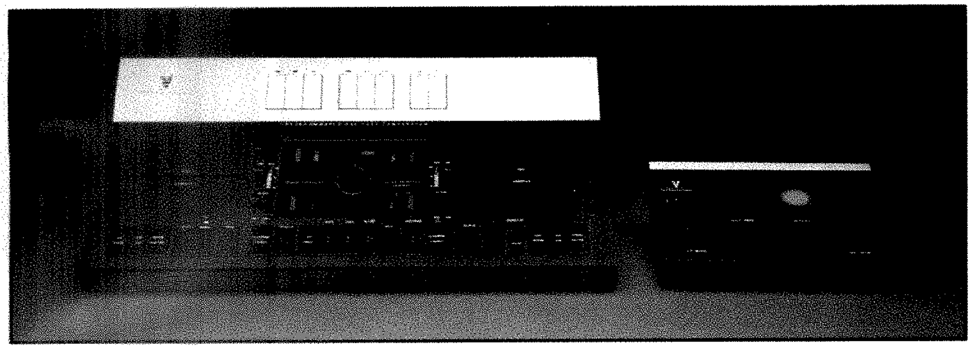

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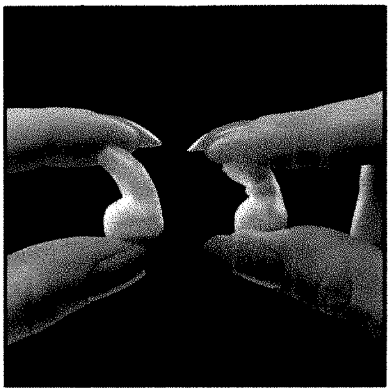

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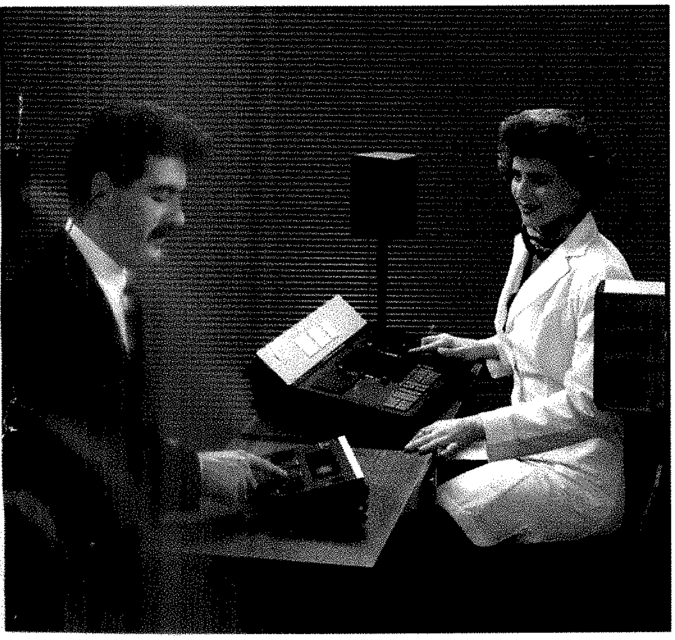

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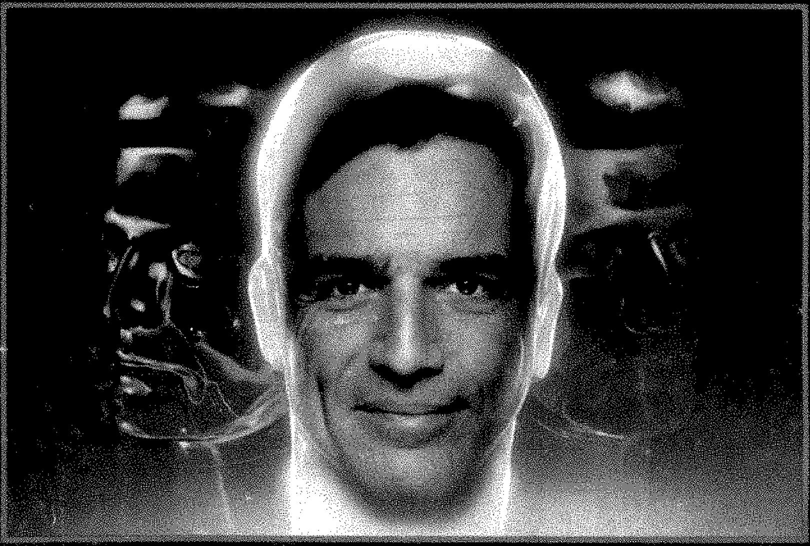

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